

**HETEROCYCLIC LITHIUM DERIVATIVES,
with particular regard to
the syntheses and reactions of iodonium salts**

Boris Holm

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HETEROCYCLIC LITHIUM DERIVATIVES, WITH PARTICULAR REGARD TO
THE SYNTHESSES AND REACTIONS OF IODONIUM SALTS

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SUMMARY

Following a presentation of the problem in chapter I and a literature survey in chapter II, the preparation of halogenated thiophenes is described in chapter III. It was here found that N-chlorosuccinimide (NCS) and N-bromosuccinimide (NBS) are good and sometimes superior alternatives to the use of molecular chlorine and bromine for the preparation of thiophenes containing mixed halogens. Product distributions are given for the reactions of NCS and NBS with different halogenated thiophenes. In addition to the use of NCS and NBS, molecular bromine and the iodine-HIO₃ methods have been utilized in efforts to synthesize halogenated thiophenes. The mechanism in the reactions of NCS and NBS is also discussed.

In chapter IV the results from the halogen metal interconversion reactions of α -bromo- β -iodothiophenes are discussed. It was found that a β -iodine reacts faster than an α -bromine with alkyllithium, but that the obtained α -bromo- β -thienyllithium intermediates were very prone to undergo rearrangement at -70° . This rearrangement process could, however, be suppressed if the halogen-metal exchange reaction was performed at temperatures below -100° . At this lower temperature, 2-bromo-3-thienyllithium could be trapped by carbon dioxide to give 2-bromo-3-thiophene-carboxylic acid. It was also found that 2-bromo-4-thienyllithium was even more unstable than 2-bromo-3-thienyllithium at -100° . In connection with the preparation of 2-bromo-3-thienyllithium, the eventual intermediacy of dehydrothiophene was investigated. However, no indications for the existence of dehydrothiophene were obtained.

Contrary to the α -bromo- β -thienyllithia, it was found, that α -chloro- β -thienyllithia were stable at -70° to -50° , and that different thiophene compounds could be prepared via such lithium derivatives. At higher temperatures, however, the α -chloro- β -thienyllithium intermediates underwent rearrangement to the more stable 2-chloro-5-thienyllithium or ring-opened to acetylenic compounds.

Syntheses and reactions of iodonium salts are described in

chapter V. It was found that unsymmetrical iodonium salts such as phenyl-thienyl-, mesityl-thienyl-, and p-anisyl-thienyl-iodonium chlorides led to substitution predominantly on the benzenic carbon in the reactions with sodium nitrite and methoxide. In the reactions with methoxide ion, the formation of unsubstituted arenes accompanied the expected substitution reactions. This latter side-reaction most probably follows a radical mechanism.

The reactions with symmetrical dithienyliodonium salts were more successful, and good yields of nitro- and thiocyanothio-phenes could be isolated upon reaction with nitrite and thiocyanate ions. Compounds such as 3-thienyl-phenyl ether, and 3-thienyl-phenyl sulphide could be obtained from reactions of di-(3-thienyl)iodonium chloride with nucleophiles.

The observation that 1,1-diphenylethylene and copper salts catalyze the reaction between iodonium salts and certain nucleophiles, made it possible to extend the amount of useful nucleophiles to e.g. cyanide and alkoxide ions. Piperidine could also be arylated to piperidinothiophene in copper catalyzed reactions. These catalyzed reactions are discussed in some detail.

Some of the successful reactions with dithienyliodonium salts were extended to difuryl- and diselenienyliodonium salts. In this way it was possible to synthesize 2-methoxy-, 2-nitro-, 3-nitro-, and 3-thiocyanofuran in addition to 2-nitro-, 3-nitro-, and 3-thiocyanoselenophene. The products isolated from the reactions of iodonium salts are obtained free of isomers.

This reaction made it also possible to synthesize the hitherto unknown 3-nitro-2-furfural from which 1-(3'-nitro-2'-furfurylideneamino)hydantoin was prepared. In contrast to its 2-nitro isomer, a well known antibacterial agent, the 3-isomer showed no activity.

In connection with a discussion on the reaction mechanism of iodonium salts and nucleophiles, the results from CIDNP experiments are compared. It was observed that the reactions between di-(3-thienyl)iodonium salts and alkoxides gave rise to CIDNP effects.

The analytical methods used and the experimental details are given in chapter VI.

I. PRESENTATION OF THE PROBLEM

The purpose of this work was threefold. Firstly, to investigate if N-chlorosuccinimide (NCS) and N-bromosuccinimide (NBS) could be appropriate reagents for the synthesis of thiophenes containing mixed halogens, since direct halogenation with molecular halogens in certain cases causes halogen-halogen substitution. Secondly, to investigate the reactions of alkyl-lithium with thiophenes containing mixed halogens, in order to determine relative reaction rates of the halogens in different positions, stabilities, and eventual rearrangements of the intermediate lithium derivatives.

The third and main purpose of this work was to see if iodonium salts prepared via lithium derivatives could be appropriate intermediates for the synthesis of those furans, thiophenes and selenophenes, which are difficult to obtain directly from the lithium derivatives or by other methods.

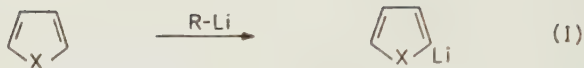
II. LITERATURE SURVEY

Since Gilman and Shirley found that thiophene with n-butyllithium gave 2-thienyllithium,¹ heterocyclic lithium derivatives, prepared by metalation of the parent arenes or by halogen-metal exchange reactions of preferably bromo or iodo derivatives, have been found to be very useful for the syntheses of several furans,^{2,3} thiophenes,^{4,5} selenophenes,^{4,5} and tellurophenes.⁷

When one of the above mentioned mother heterocycles is treated with alkylolithium, a 2-substituted derivative is obtained (I). The 3-substituted isomers are prepared at low temperature from a 3-bromo or 3-iodo derivative (II).

Using this method Gronowitz obtained 3-thienyllithium⁸ from 3-bromothiophene,⁹ opening a way to several 3-substituted thiophenes and other substituted five-membered heterocycles.

Lithium compounds afford excellent intermediates for the introduction of different substituents, as exemplified below for thiophene (III).



X = O; S; Se; Te

Y = Br; I



X = CO₂; HCON(CH₃)₂; S; R-S-S-R; Cl₂; Br₂; I₂; R₂CO; (CH₃O)₂SO₂

Y = COOH; CHO; SH; S-R; Cl; Br; I; R₂COH; CH₃

Most of the reactions above are also easily performed with the furan and selenophene analogues, but in the tellurophene case only 2-telluriényllithium⁷ has been prepared due to the present inavailability of 3-bromo- and 3-iodotellurophene (upon halogenation the tellurium atom is attacked¹⁰).

Some 3-lithiated furans¹¹ and selenophenes^{12,13} are unstable even at -70° and undergo ring-opening reactions; however, they can still be used as valuable synthetic reagents.^{14,15}

The most widely used methods for the preparation of the halogenated heterocycles in question can in short be summarized as follows.

Steinkopf and Köhler showed that it was possible to obtain several chlorinated thiophenes via mercury intermediates.¹⁶ It has also been stated that it was possible to brominate 3-iodothiophene but not the 2-isomer, and that chlorination of iodothiophenes failed with both iodo isomers.¹⁷ In the unsuccessful

ful reactions the iodine atom was substituted for chlorine or bromine.

If N-chlorosuccinimide (NCS) and N-bromosuccinimide (NBS) are used as halogenating agents, instead of chlorine and bromine, respectively, it will be shown in this work that the above statements are true with some modification.

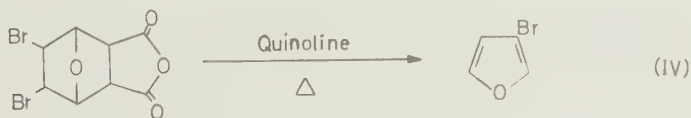
Campaigne and LeSuer¹⁸ found that thiophene and sulphuryl chloride gave 2- and 2,5-dichlorothiophene.

Bromination of thiophene is performed with bromine in solvents such as acetic acid, chloroform and carbon tetrachloride. In this way 2-,¹⁹ 2,5-di,¹⁹ 2,3,5-tri-²⁰ and tetrabromothiophene²¹ are easily obtained. Dioxane dibromide brominates thiophene in quantitative yield.²² 3-Bromo- and 3,4-dibromothiophene are best prepared by dehalogenation of 2,3,5-tri- and tetrabromothiophene, respectively.⁹

The iodination of thiophene is most conveniently performed with iodine and HIO_3 , giving 2-iodothiophene in 75 % yield.²³ This method has also been used for the preparation of 2,3-di- and 2,3,5-triiodothiophene.²⁴ An advantage of this method, over that via mercury derivatives,²⁵ is that better yields are generally obtained, mercury compounds can be avoided, and all the iodine is utilized.

Concerning the halogenation of furan and selenophene, the following aspects are to be considered.

Direct halogenation of furan is a vigorous process and the desired products are often accompanied by polymerization due to the liberation of hydrogen halide.²⁶ Furan can however be brominated with dioxane dibromide at 0° to give 2-bromofuran in good yield.²² 3-Bromofuran is obtained in a sequence starting from 2-furoic acid via 2,3-dibromo-5-furoic acid and 2,3-dibromofuran, followed by halogen-metal exchange of the latter^{27,28} or, alternatively, in a retro Diels-Alder process of *exo-cis*-3,6-*endo*-4,5-dibromotetrahydrophthalic anhydride (IV).²⁹

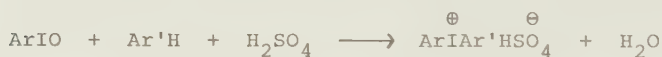


Both 2-iodofuran^{30,31} and the 3-isomer³² have been prepared from the corresponding chloromercurifurans and potassium iodide. 2-Halofurans are very unstable even at room temperature, while the 3-analogues are more stable,³² and the latter are thus appropriate starting materials for other furans.

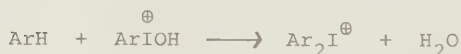
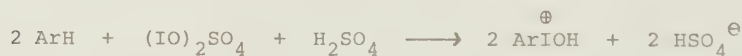
Selenophene reacts with halogens as thiophene and the corresponding halogenated selenophenes are easily obtained.³³

The first iodonium salt, p-iodophenyl-phenyliodonium bisulphate, was discovered by Hartmann and Meyer.³⁴ Lucas and Kennedy prepared diphenyliodonium iodide from iodosobenzene and iodoxybenzene in the presence of sodium hydroxide and treatment with potassium iodide.³⁵ Iodonium salts were only sporadically investigated, until Beringer *et al.*³⁶ in 1953 published their first paper about their extensive work on the synthesis and reactions of different diphenyliodonium salts. The most important synthetic procedures for iodonium salts are:

- A) Iodo disalts, iodoso and iodoxy compounds undergo acid-catalyzed condensation with aromatic hydrocarbons.³⁶



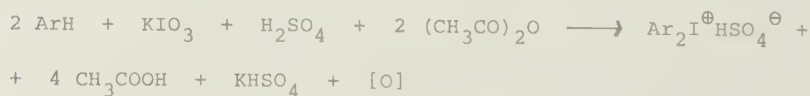
- B) Iodosyl sulphate and aromatic hydrocarbons in sulphuric acid give symmetrical iodonium salts.³⁶



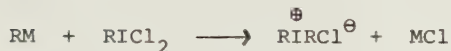
- C) Iodine (III) acylates³⁷ react with hydrocarbons in an acid-catalyzed reaction.³⁸



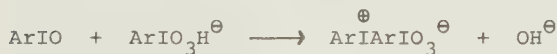
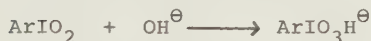
- D) Aromatic hydrocarbons and sodium or potassium iodate in acetic acid-acetic anhydride-sulphuric acid.³⁶



E) Iodine trichloride reacts with organometallic compounds in a three-step process.^{39,40}



F) Base-catalyzed condensation of a mixture of iodoso and iodoxy compounds gives iodonium salts.³⁴⁻³⁶



In one publication⁴¹ several salts have been prepared by utilizing methods A, B, C, and D. As indicated above, this work deals with the second step in the reaction scheme of method E. Only aryllithium compounds have been used as the organometallic intermediates for the syntheses of iodonium salts. By this method Beringer *et al.* found, that if arylidoso dichloride was treated with one equivalent of aryllithium both symmetrical and unsymmetrical salts could be obtained,³⁹ and that additional-



ly two equivalents of aryllithium react with trans-chlorovinyl-iodoso dichloride, giving symmetrical iodonium salts.⁴²



By this latter reaction they also prepared di-(2-furyl)- and di-(2-thienyl)iodonium iodide.⁴³

Diphenyliodonium salts have been shown to be good arylating agents for different nucleophiles such as alkoxide, phenoxide, cyanide, nitrite, and amines⁴⁴ as well as anions of e.g. dimedone and benzoylmethanes.⁴⁵

In this thesis the reactions between iodonium salts containing at least one heterocyclic ring and different nucleophiles will be discussed.

For a deeper and broader introduction to the halogenation of heterocyclic compounds, the interested reader is referred to Ref. 46; Ref. 47 takes up the use of lithium intermediates and Refs. 48 and 49 deal with polyvalent iodine compounds.

DISCUSSION

III. HALOGENATED THIOPHENES

III.1 Introduction

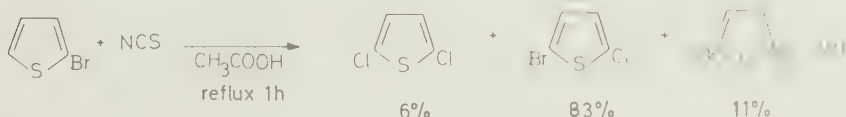
As mentioned in the literature survey, halogenated thiophenes are starting materials for several lithiated thiophenes, which in turn are intermediates for the synthesis of other compounds. Because of this it was of interest to synthesize thiophenes containing mixed halogens and to study the stabilities and eventual rearrangements of different thienyllithium derivatives. Since it had been found that when molecular chlorine or bromine are used as halogenating agents, the most electronegative halogen should be introduced first if thiophenes with mixed halogens are to be prepared,¹⁷ it was decided to investigate if NCS and NBS would behave in a similar fashion. In connection with this, the determination of the product distributions was also of interest.

In addition to the syntheses of the halogenated thiophenes in this chapter some others will be described in connection with the reactions of thienyllithia (cf. chapter IV).

III.2 Chlorination with N-chlorosuccinimide

2-Bromo-5-chlorothiophene⁵⁰ is most conveniently obtained by bromination of 2-chlorothiophene¹⁸ and 2-chloro-5-iodothiophene, such as will be described in this work, by iodination of 2-chlorothiophene using iodine and iodic acid (HIO₃).

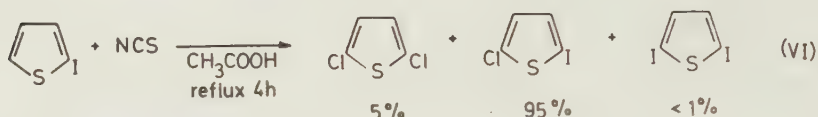
When 2-bromothiophene¹⁹ was treated with one equivalent of NCS in acetic acid, vpc analysis (column A) gave the following product distribution:*



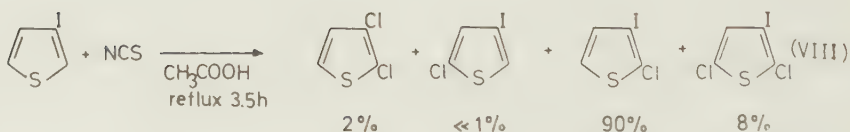
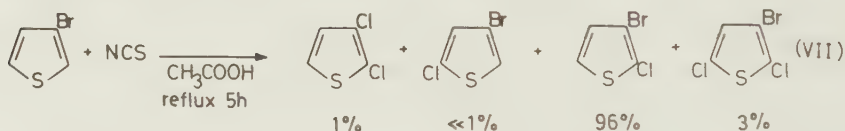
* Relative concentrations of products normalized to 100 %.

In a preparative run 55 % of 2-bromo-5-chlorothiophene could be isolated.

2-Iodothiophene²³ could also be chlorinated with NCS (column A):



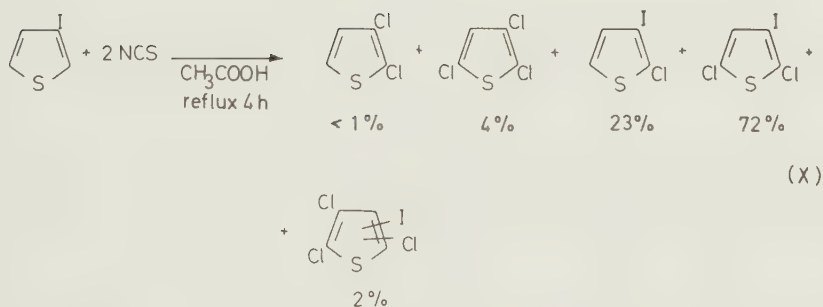
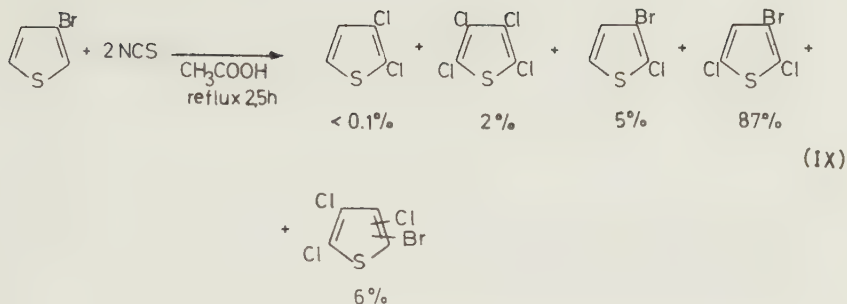
With one equivalent of NCS, 3-bromo-⁹ and 3-iodothiophene⁵¹ were predominantly chlorinated in the 2-position (column A):



The sensitivity factor of 2,3-dichlorothiophene was set equal to that of 2,5-dichlorothiophene.

3-Bromo-2-chlorothiophene was prepared independently of another work in which the same method was used.⁵²

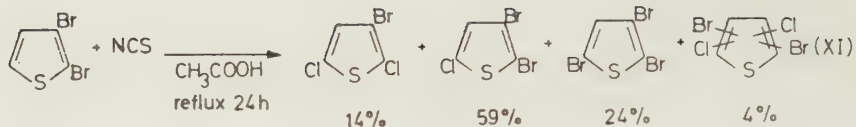
Two equivalents of NCS gave in the same way (column A):



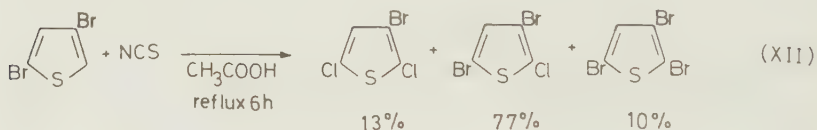
In the reactions above, the obtained monobromo-trichloro- and monoiodo-trichlorothiophenes were not identified as to which isomers prevailed, and their sensitivity factors to the gas chromatographic flame were set equal to 3-bromo-2,5-dichloro- and 2,5-dichloro-3-iodothiophene, respectively.

It can be mentioned that if sulphuryl chloride was allowed to react with 3-bromothiophene,⁹ a great number of products were obtained. None of the products was dominating and no effort to identify them was made. Thus it appears that sulphuryl chloride is not a suitable reagent for preparing halogenated thiophenes; this was also demonstrated in that sulphuryl chloride and 2,3-diiodothiophene²⁴ did not give 5-chloro-2,3-diiodothiophene.

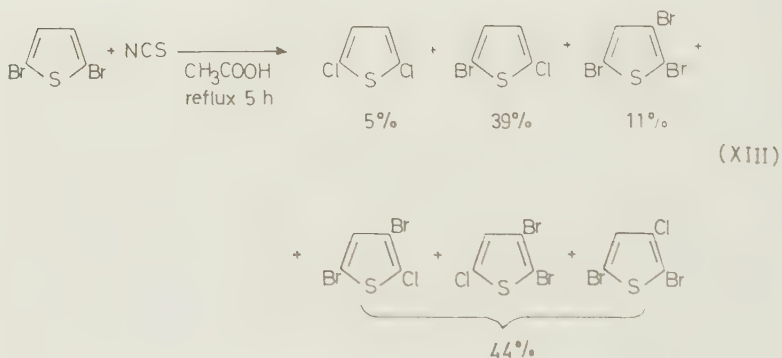
2,3-Dibromothiophene⁵³ and NCS (1:1) gave the following result (column B):



The dibromo-dichlorothiophene was not identified and its sensitivity factor was set equal to 3-bromo-2,5-dichlorothiophene. Analogously, 2,4-dibromothiophene⁵⁴ and NCS (1:1) gave (column B):



An attempt to chlorinate 2,5-dibromothiophene¹⁹ with NCS (1:1) was unsuccessful (column C):



No column was found, which separated the isomeric dibromo-monochlorothiophenes. While it is possible that not all three products were formed, analysis showed that the actual peak in the gas chromatogram contained at least two products. The values above are not calibrated.

As a conclusion, it is shown that NCS can chlorinate several bromo- and iodothiophenes without excessive substitution of the less electronegative halogens. In Table 1 the yields in preparative runs are listed.

Table 1. Reactions between halogenated thiophenes and NCS in acetic acid at reflux.

Reactant (thiophene)	Product (thiophene)	Yield (%)
2-Bromo- ^a	2-Bromo-5-chloro-	55
2-Iodo- ^a	2-Chloro-5-iodo-	55
3-Bromo- ^a	3-Bromo-2-chloro-	62
3-Iodo- ^a	2-Chloro-3-iodo-	53
3-Bromo- ^b	3-Bromo-2,5-dichloro-	55
3-Iodo ^b	2,5-Dichloro-3-iodo	39
2,3-Dibromo- ^a	5-Chloro-2,3-dibromo-	36
2,4-Dibromo- ^a	2-Chloro-3,5-dibromo-	43

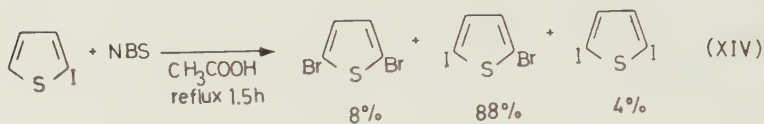
^a1 equivalent of NCS.

^b2 equivalents of NCS.

It should be noted that the yields in Table 1 were in some cases obtained if NCS was used in about 5 % excess; it was found that a slight excess of NCS raised the yields of the desired products, since if NCS was added in exact equality with the thiophene not all of the starting material was consumed. The discrepancy between isolated yields given in Table 1 and the yields determined by gas chromatographic analyses can be attributed to decomposition of formed products during the progress of the reaction, losses in connection with the separation of formed products, and in some cases to small amounts of unreacted starting material. These differences also hold for the experiments carried out with NBS (cf. below).

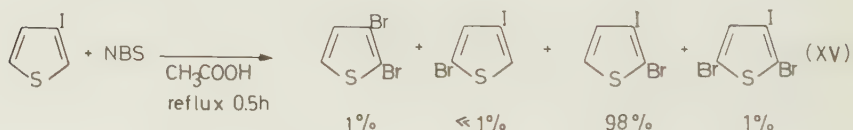
III.3 Bromination with N-bromosuccinimide

If NBS was used as brominating agent it was possible to brominate 2-iodothiophene²³ (column C):

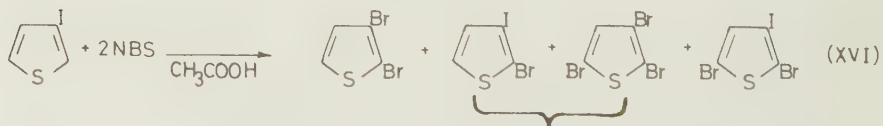


If 2-iodothiophene was treated with two equivalents of NBS either at room temperature or at reflux, the main product was 2,5-dibromothiophene together with traces of 2-bromo-5-iodothiophene and other more high-boiling products, which were not characterized. This indicates that the second bromine prefers to eliminate the iodine instead of entering a β -position.

2-Bromo-3-iodothiophene⁵⁵ was obtained from 3-iodothiophene⁵¹ and NBS (1:1) (column A):



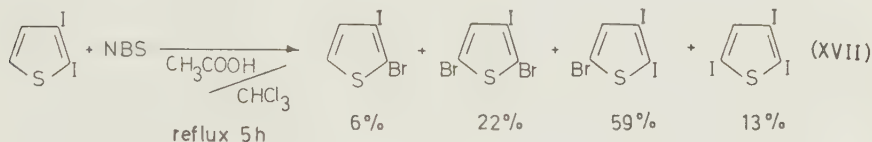
With two equivalents of NBS, 2,5-dibromo-3-iodothiophene was the main product. Here it was found that the reaction time and temperature had a great influence on the product distribution (column A, C):



Room temp.	19 h	1 %	9 %	90 %
Reflux	2 h	2 %	23 %	75 %
Reflux	5 h	2 %	29 %	69 %

As is seen in scheme XVI, the best result was obtained at room temperature. That at reflux, a prolonged reaction time did not favor the yield of 2,5-dibromo-3-iodothiophene can probably be ascribed to decomposition of this product at higher temperatures. The separation of the products with vpc was not possible, and therefore no calibration was made.

2,3-Diiodothiophene²⁴ and NBS (1:1) in acetic acid:chloroform (1:1) gave the following product distribution (column B):



If only acetic acid is used as solvent, the deviation of the result is very small. Variation of the reaction temperature did not increase the yield of 5-bromo-2,3-diiodothiophene.

In Table 2 the yields in preparative experiments with NBS are given. From these results, it is evident that NBS represents a useful reagent for the synthesis of various bromoiodothiophenes.

Table 2. Reactions between halogenated thiophenes and NBS in acetic acid at reflux.

Reactant (thiophene)	Product (thiophene)	Yield (%)
2-Iodo- ^a	2-Bromo-5-iodo-	38
3-Iodo- ^a	2-Bromo-3-iodo-	83
3-Iodo- ^b	2,5-Dibromo-3-iodo-	44
2,3-Iodo- ^a	5-Bromo-2,3-diiodo-	5

^a1 equivalent of NBS.

^b2 equivalents of NBS.

In addition to the results above it can be mentioned that 2-bromo-5-chlorothiophene was the product upon reaction of 2-chlorothiophene¹⁸ with NBS. As with NCS it was sometimes advantageous to use a small excess of NBS.

III.4 Halogenation with bromine and iodine

When 3-iodothiophene⁵¹ was allowed to react with two equivalents of bromine in carbon tetrachloride, the main part of the products consisted of a hexabromobithienyl or a mixture of hexabromobithienyls together with 2,3,5-tribromothiophene. The isomeric identity of the hexabromobithienyls were not determined, since it was outside of this work and could be expected to be very time consuming. 2,5-Dibromo-3-iodothiophene could not be detected in the reaction mixture.

If acetic acid was used as solvent the products were mainly 2,5-dibromo-3-iodothiophene together with 2,3,5-tribromothiophene. In this case no hexabromobithienyl was obtained.

The best route to 2,5-dibromo-3-iodothiophene seems to be to dibrominate 3-iodothiophene⁵¹ with NBS (see Table 2); the iodination of 2,5-dibromothiophene¹⁹ with iodine-HIO₃ gave only an 11 % yield of the desired product.

The bromination of 2,3-diiodothiophene²⁴ with bromine in carbon tetrachloride was unsuccessful. Several products were obtained, but no 5-bromo-2,3-diiodothiophene could be detected. No product was dominating and no identification was made.

If 2-bromo-3-iodothiophene⁵⁵ was iodinated with iodine and HIO₃, 2-bromo-3,5-diiodothiophene was isolated in 53 % yield. By the same method it was possible to iodinate 3-bromothiophene⁹ to give 3-bromo-2-iodothiophene. Likewise 2-chlorothiophene¹⁸ gave 2-chloro-5-iodothiophene.

III.5 Conclusions of the halogenation reactions

As shown above, NCS and NBS are good alternatives to molecular chlorine and bromine as halogenating agents. A great advantage of NCS and NBS is their selectivity of attack, which can e.g. be seen by the reactions of bromo- and iodothiophenes (cf. VI-VIII, XIV, XV). The main products obtained in

VII, VIII, and XV have arisen from substitution in the 2-position; the concentration of the expected by-product, from substitution in 5-position, is very low.

The selectivity in halogenating reactions has earlier been demonstrated by Gronowitz and Karlsson,⁵⁶ who found that the iodination of 3-iodothiophene with iodine and iodic acid gave 99.5 % of 2,3-diiodothiophene and 0.5 % of 2,4-diiodothiophene. In other investigations⁵⁷ it was found that bromination of 3-phenylthiophene with NBS in carbon tetrachloride led almost exclusively to 2-bromo-3-phenylthiophene, while NBS in acetic acid⁵⁸ gave a mixture of the 2- and 5-isomer. Bromine in acetic acid⁵⁷ yielded 5-bromo-3-phenylthiophene (70 %) and 2-bromo-3-phenylthiophene (30 %). Here again it was found that the change of solvent had a great influence on the reaction path, with bromine in carbon tetrachloride⁵⁸ giving 99 % of 2-substitution and only 1 % of 5-substitution.

Bromination of 2-phenylthiophene with bromine in acetic acid⁵⁹ was also found to be a selective reaction, giving 5-bromo-2-phenylthiophene (96 %) and 3-bromo-2-phenylthiophene (4 %).

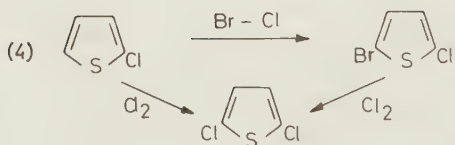
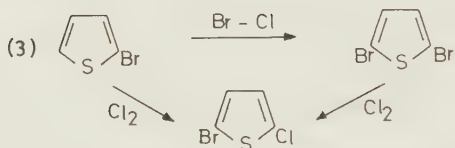
These results, together with those described in this thesis, show that NCS and NBS very often are versatile reagents for the synthesis of compounds containing low contaminations in the form of isomers. Besides their selectivity of substitution, it has been shown in this work that it is possible to chlorinate and brominate different bromo- and iodothiophenes with NCS and NBS, which was difficult to achieve when molecular chlorine and bromine were used.¹⁷ Another advantage of NCS and NBS is that these reagents are more easily added in an exact quantity than chlorine and bromine.

The reason for the production of 2,5-dibromo-, 2,5-dichloro-, 2,5-diiodo-, 2,3,5-tribromo-, and 2,3,5-triiodothiophene in e.g. (V), (VI), (XI), and (XVII) can be explained by assuming that molecular chlorine and bromine are generated initially in a radical reaction from NCS or NBS and traces of hydrogen chloride and hydrogen bromide respectively.⁶⁰ These molecular halogens then go into aromatic electrophilic substitution reactions, leading to exchange of the less electronegative halogen for the more electronegative one.

In this way Br-Cl, I-Cl, and I-Br are generated and these latter species then enter into electrophilic reactions, where the least electronegative halogen becomes bound to the thiophene ring as illustrated for 2-bromothiophene (XVIII).



(XVIII)



The main part of the 2-bromo-5-chlorothiophene is thought to be formed in a normal electrophilic substitution reaction of 2-bromothiophene and chlorine. 2,5-Dibromothiophene can undergo a substitution reaction with chlorine to give 2-bromo-5-chlorothiophene, which upon further reaction with chlorine gives 2,5-dichlorothiophene. This latter product is alternatively produced from chlorination of 2-chlorothiophene. The products from the reactions of NBS can be explained by an analogous reaction scheme.

It can be mentioned that the product distributions in reactions (V)-(XVII) were reproducible in 2-3 %.

IV. THIENYLLITHIUM DERIVATIVES

In chapter II of this thesis a short description was made on the use of alkyllithium derivatives for the conversion of aryls into lithiated compounds. Because several thiophenes containing mixed halogens had been synthesized, it was of interest to see how such compounds would behave with alkyllithium. Previously little work had been carried out on the reaction between alkyllithium and thiophenes containing mixed halogens. In connection with these reactions two main questions were addressed, 1) could thiophenes with mixed halogens be used as starting materials for other thiophenes and 2) what were the stabilities and rearrangements of the thienyllithium intermediates?

From earlier investigations it was known that the reaction between bromothiophenes and alkyllithium is very rapid.⁶¹ It was also known that an α -bromine exchanges much more rapidly than a β -bromine. This was, e.g., demonstrated in the halogen-metal exchange reaction between 2,3-dibromo- and 2,4-dibromothiophene with n-butyllithium at -70° , in which cases only the α -halogen was exchanged.⁶¹ In the classical investigations of Wittig et al. and Gilman et al. it was shown that iodides react more rapidly than bromides (for a review, see Ref. 62). Because of these facts, it was of interest to study the halogen-metal exchange reaction of 2-bromo-3-iodothiophene and ethyllithium to determine which factor would dominate.

In connection with the halogen-metal exchange of 2-bromo-3-iodothiophene, the question of the existence of dehydrothiophene was likewise a fascinating point. Gronowitz et al. had before showed the high stability of ortho bromothiennyllithium derivatives such as 3-bromo-2-thienyllithium.⁶³ In contrast to ortho bromophenyllithium,⁶⁴ these compounds showed no tendency to split out lithium bromide to give dehydrothiophene. Likewise it was found that 3-fluoro-2-thienyllithium, obtained through metalation of 3-fluorothiophene, was stable and no dehydrothiophene could be trapped by furan.⁶⁵ The Grignard route from 3-fluoro-2-bromofuran was also unsuccessful for the

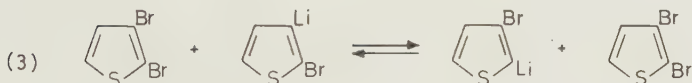
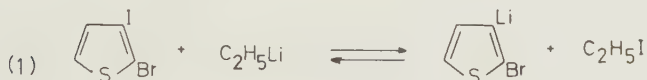
production of 2,3-dehydrothiophene.

A paper by Wittig and Rings describes their efforts to prove the intermediate formation of dehydrothiophene.⁶⁶ They found that neither 3-bromo-2-thienyllithium nor 2,5-diphenyl-4-iodo-3-thienyllithium nor mercury compounds such as bis[3-iodo-2-thienyl]mercury gave dehydrothiophene. Reinecke and Adickes⁶⁷ showed that the ciné-substitution reaction between 2-bromothiophene and potassium amide in liquid ammonia does not go via a dehydrothiophene, but has its explanation in a series of transbrominations similar to those observed by Gronowitz and coworkers in the reaction of 3-bromo- and dibromothiophenes with n-butyllithium.⁶¹ The hope was that if 2-bromo-3-thienyllithium was formed in the halogen-metal exchange reaction of 2-bromo-3-iodothiophene, this ought to be the hitherto most suitable intermediate studied for the production of 2,3-dehydrothiophene.

When 2-bromo-3-iodothiophene was treated with ethyllithium at -70° , keeping the temperature below -60° , the product distribution showed the following composition after protonation with ethanol: 3-iodothiophene (20 %), 3-bromothiophene (55 %), 2-bromothiophene (5 %), and 2,3-dibromothiophene (20 %). Carbonation of a corresponding reaction mixture yielded an acid mixture, which was esterified with diazomethane and analyzed by vpc. This analysis showed the formation of methyl 3-iodo-2-thiophenecarboxylate (26 %), 3-bromo-2-thiophenecarboxylate (71 %) and 2-bromo-3-thiophenecarboxylate (3 %). The analysis indicated that the pure halothiophenes (except 2,3-dibromothiophene) obtained upon hydrolysis exist as lithiated derivatives. Formation of 3-bromo-2-thienyllithium was an unexpected observation, and it would be attractive to explain its generation from initially formed 2-bromo-3-thienyllithium, which splits off lithium bromide to give dehydrothiophene, followed by addition of lithium bromide in the opposite direction to give the more stable thienyllithium derivative. However, all attempts to catch the intermediate 2,3-dehydrothiophene with furan failed. An alternative explanation can therefore be proposed. It seems likely that initially formed 2-bromo-3-thienyllithium undergoes a series of rapid halogen-metal exchange reactions even at -70° , leading to the most stable lithium derivative. This tendency has

earlier been observed for 4-bromo-3-thienyl- and 4-bromo-2-thienyllithium.⁶¹

The following transformation scheme can be proposed:⁵⁵



The non-existence of lithiated 2,3-dibromothiophene is in accordance with earlier results,⁶¹ which showed that 2,3-dibromothiophene is not metalated at such a low temperature. The hope was that the rearrangement of the primary halogen-metal exchange product could be suppressed by keeping the temperature below -100° . This was found to be the case. If a 50 % excess of ethyllithium was used, and the temperature kept below -100° during the addition, vpc showed after addition of ethanol a product distribution of 2-bromothiophene (95 %), 3-bromothiophene (5 %), and 3-iodo- and 2,3-dibromothiophene (less than 1 %). The same reaction showed after carbonation and esterification, as above, the formation of methyl 2-bromo-3-thiophenecarboxylate (84 %), 3-bromo-2-thiophenecarboxylate (5 %), and 3-iodo-2-thiophenecarboxylate (11 %). In the carbonation reaction it is necessary to add the dry ice carefully to avoid a rise in temperature. After recrystallization of the crude product from water-ethanol (1:1), pure 2-bromo-3-thiophenecarboxylic acid was obtained in 46 % yield. Halogen-metal exchange between 2-bromo-3-iodothiophene and ethyllithium below -100° is thus an alternative to the four-step synthesis, developed by Campaigne and LeSuer,⁶⁸ which starts from 3-methyl-

thiophene and via 2-bromo-3-methylthiophene, 2-bromo-3-thenyl bromide and 2-bromo-3-thenaldehyde leads to 2-bromo-3-thiophene-carboxylic acid.

If only a 10 % excess of ethyllithium is used at -110° the amount of 3-iodo-2-thienyllithium, as well as of 3-bromo-2-thienyllithium, increases and 2,3-dibromothiophene appears. An explanation of this behavior can be that 3-iodo-2-thienyllithium is not formed in direct halogen-metal exchange with ethyllithium, but in step 2 in reaction scheme XIX.

It was also found that a large excess (200 %) of ethyllithium suppressed the rearrangement of 2-bromo-3-thienyllithium and lowered the amount of 3-iodo-2- and 3-bromo-2-thienyllithium produced. However, the total yield of halothiennyllithium decreased, due to the formation of dilithiated product, as verified by the observation of thiophene upon hydrolysis.

Authentic samples of 2-bromo-,¹⁹ 3-bromo-,⁹ 2,3-dibromo-,⁵³ and 3-iodothiophenes,⁵¹ as well as of 3-bromo-2-thiophenecarboxylic acid,⁶¹ were used for identification of the obtained products. 3-Iodo-2-thiophenecarboxylic acid was prepared separately.

Since 2-bromo-3-iodothiophene had been found to undergo rapid rearrangement reactions upon treatment with ethyllithium, it was of interest to investigate if 2-bromo-4-iodothiophene would behave in the same manner. A possible route to 2-bromo-4-iodothiophene was to effect halogen-metal exchange on 5-bromo-2,3-diiodothiophene, which should then give the desired compound after hydrolysis. The preparation of 5-bromo-2,3-diiodothiophene was, however, difficult due to the low yield from the bromination of 2,3-diiodothiophene²⁴ as described in chapter III. Therefore, an alternative route to 2-bromo-4-iodothiophene was sought; when 2,4-diiodothiophene,²⁴ after reaction with alkyllithium, was treated with bromine 2-bromo-4-iodothiophene was obtained in 36 % yield. Since it had been shown that 2-bromo-3-iodothiophene exchanged iodine faster than bromine it was suspected that 2,5-dibromo-3-iodothiophene should react in a similar fashion. It was also found that the reaction mixture of 2,5-dibromo-3-iodothiophene and *n*-butyllithium contained several products, with their origin in rearrangement reactions. Thus it was here further indicated that a β -iodine

exchanges faster than an α -bromine in halogen-metal exchange reactions; thus, this did not represent a route to 2-bromo-4-iodothiophene.

When 2-bromo-4-iodothiophene was allowed to react with n-butyllithium it was found that the intermediate 2-bromo-4-thienyllithium was more unstable than 2-bromo-3-thienyllithium and underwent rapid rearrangement, even at -100° . The results were here also somewhat more difficult to reproduce, and in Table 3 the analytical results obtained in the same manner as with 2-bromo-3-iodothiophene are given.

From Table 3 it is seen that a large excess of alkyl-lithium suppresses the rearrangement of initially formed 2-bromo-4-thienyllithium. The observation of methyl 3,5-dibromo-2-thiophenecarboxylate at below -100° in one case was somewhat astonishing, in regard to the fact that metalation is a slow process at such a low temperature, but it is in accordance with earlier results, where it was found that 2,4-dibromothiophene is more easily metalated than 2,3-dibromothiophene.⁶¹ Thus, 2-bromo-4-iodothiophene is obviously not a suitable starting material for 2-bromo-4-thiophenecarboxylic acid, prepared in good yield by the bromination of 3-thiophenecarboxylic acid.⁶⁹

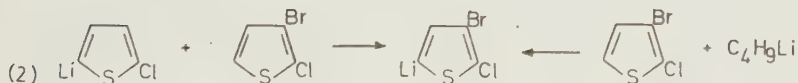
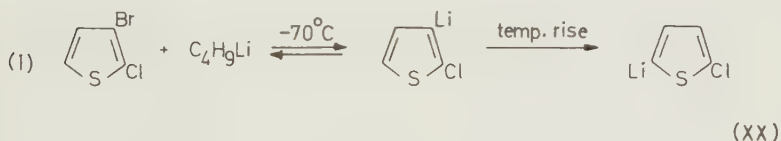
3-Bromo-2-chloro- and 2-chloro-3-iodothiophene did not show any tendency to rearrangement when treated with alkyl-lithium at -70° , in contrast to the above described bromo-iodothiophenes. Protonation of the intermediate 2-chloro-3-thienyllithium gave only 2-chlorothiophene, while carbonation gave 2-chloro-3-thiophenecarboxylic acid in good yield.

4-Bromo-2-chlorothiophene can be prepared from 4-bromo-2-thienyllithium upon reaction with chlorine⁷⁰ or with hexachloroethane.⁷¹ Since 5-chloro-2,3-dibromothiophene already had been prepared, this compound was allowed to react with butyllithium to give 4-bromo-2-chlorothiophene in 53 % yield. When 4-bromo-2-chlorothiophene in turn was reacted with alkyl-lithium, 2-chloro-4-thiophenecarboxylic acid was obtained after carbonation and 2-chloro-4-iodothiophene after the addition of iodine. Even in this case, no rearrangement products could be observed if the reaction was carried out at -70° .

Table 3. Product distributions in the reactions of 2-bromo-4-iodothiophene with n-butyllithium in ether after protonation or carbonation followed by acidification and esterification.

Temp. (°C)	2-Bromo- thiophene (%)	3-Bromo- thiophene (%)	3-Iodo- thiophene (%)	2,4-Dibromo- thiophene (%)	Excess of <u>n</u> -BuLi (%)
< - 60	8	48	39	5	110
< - 60	66	22	11	trace	150
< -100	9	24	35	33	10
< -100	60	trace	19	21	10
< -100	24	12	32	32	10
	Methyl 2-bromo- 4-thiophene- carboxylate (%)	Methyl 4-bromo- 2-thiophene- carboxylate (%)	Methyl 4-iodo- 2-thiophene- carboxylate (%)	Methyl 3,5-di- bromothiophene- carboxylate (%)	
< - 60	trace	21	62	16	10
< -100	64	2	26	8	10
< -100	92	1	7	-	10
< -100	78	6	17	-	10

In earlier investigations it was found that 3-positioned lithium in thiophene had a tendency to rearrange, especially at higher temperatures.⁶¹ Therefore it could be expected that 2-chloro-3-thienyllithium, obtained from either 3-bromo-2-chloro- or 2-chloro-3-iodothiophene, likewise should undergo rearrangement at higher temperatures. If 2-chloro-3-thienyllithium, prepared at -70° , was allowed to reach room temperature slowly and stirred overnight it was observed that both a rearrangement and a metalation process had occurred. When the reaction was performed with 3-bromo-2-chlorothiophene and one equivalent of *n*-butyllithium the products, after carbonation, consisted of 2-chloro-5-thiophenecarboxylic acid, 2-chloro-3-thiophenecarboxylic acid and 3-bromo-2-chloro-5-thiophenecarboxylic acid. For identification, 3-bromo-2-chloro-5-thiophenecarboxylic acid was prepared from 2-chloro-3,5-dibromothiophene and alkyllithium followed by carbonation. The isomeric 3-bromo-5-chloro-2-thiophenecarboxylic acid was analogously obtained from 5-chloro-2,3-dibromothiophene.



It is not known if 3-bromo-2-chlorothiophene is metalated by 2-chloro-5-thienyllithium or *n*-butyllithium. Even if a 40 % excess of butyllithium was used the result was the same. The relative concentration of the products varied with each run (cf. Table 4). The reason for the irreproducibility of the studied reaction is unknown, but can have its explanation in small variations of the temperature and concentrations of the different thienyllithium derivatives. If 2-chloro-3-iodothiophene was used instead of 3-bromo-2-chlorothiophene the reaction mixture contained 2-chloro-5- and 2-chloro-3-thienyllithium, but no 2-chloro-3-iodo-5-thienyllithium had been formed,

Table 4. Product distributions in the reactions of 3-bromo-2-chloro- and 2-chloro-3-iodo-thiophene with butyllithium in ether at -70° followed by temperature rise, carbonation, acidification, and esterification.

Methyl 2-chloro-5-thiophene-carboxylic acid ^a (%)	Methyl 2-chloro-3-thiophene-carboxylic acid (%)	Methyl 2-chloro-3-bromo-5-thiophenecarboxylic acid (%)
18	71	10
53	5	42
31	45	23
32	68	—
25	75	—
13	87	—

^aThe sensitivity factor of methyl 2-chloro-5-thiophenecarboxylic acid was set equal to that of methyl 2-chloro-3-thiophenecarboxylic acid.

Remark: The first three results were obtained with 3-bromo-2-chlorothiophene and the following three with 2-chloro-3-iodothiophene.

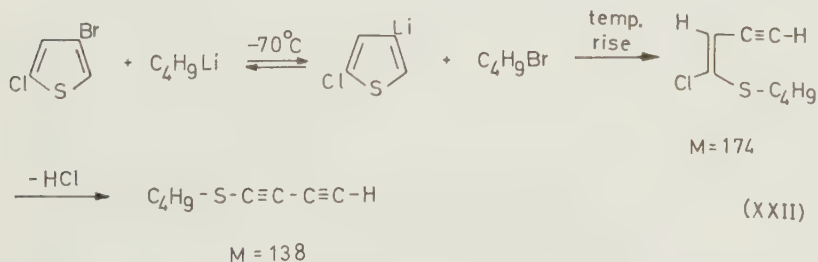
which was demonstrated by carbonation and analysis of the esterified acid mixture.

This latter observation can be explained if the equilibrium (XXI) is thought to lie more to the right if $X = I$ than



if $X = \text{Br}$, in accord with the fact that iodides undergo halogen-metal exchange more easily than bromides.⁶² As indicated by IR analysis of the reaction mixtures, 2-chloro-3-thienyllithium does not appear to ring-open to yield acetylenic compounds. Such a ring-opening is observed with other 3-thienyllithia.¹¹ The reason that 2-chloro-3-thienyllithium does not seem to ring-open can possibly be attributed to the inductive effect of chlorine.

2-Chloro-4-thienyllithium was prepared from 4-bromo-2-chlorothiophene at -70° . If this lithium derivative was stirred overnight at room temperature no chlorothiophenecarboxylic acid could be detected. On the other hand, IR analysis showed the appearance of a carbon-carbon triple bond, which can have its explanation in the presence of an acetylenic compound formed in a ring-opening process followed by the elimination of hydrogen chloride.



One peak in the gas chromatogram (column A), with longer retention time than the starting material showed (combined vpc-mass spectrometry) a molecular ion with $m/e = 138$. The mass numbers 139 and 140 were also represented and the ratio of the

intensities of the mass numbers $m/e = 138, 139, 140 = 17.3:1.86:1.00$ fits rather well with that for sulphur ($22.7:0.18:1.00$), if account is taken to the isotopic distribution of carbon. In addition to $m/e = 138$, which was the most intense fragment in mass spectrum, $m/e = 81$ and 82 were of high intensity. The fragment $m/e = 81$ can be assumed to have its origin in the elimination of a butyl group from the molecular ion ($M^+-C_4H_9 = 81$) while $m/e = 82$ is obtained if 1-buten is eliminated in an intramolecular process.

The above indications, together with the experimental fact that ring-opened products usually have longer retention times than their non-ring-opened isomers,⁷² speaks for the proposed reaction scheme (XXII), and that the compound with molecular weight 138 is butylthiodiacetylene. In this case, the bond to lithium is not stabilized by chlorine and this should, if not favor, at least not prevent the occurrence of ring-opening.

The ring-opening reactions of thiophenes were not further examined, because they are part of a broader investigation on the ring-opening of heterocyclic compounds.⁷³

An attempt to react 2-thienyllithium¹ with NCS and NBS to produce 2-chloro- and 2-bromothiophene failed; only thiophene could be detected upon hydrolysis.

From the reactions of 3-bromo-2-chloro-, 2-chloro-3-iodo-, and 4-bromo-2-chlorothiophene with alkyllithium, it is obvious that α -chloro- β -thienyllithia are relatively stable, since at low temperature no rearranged products were obtained upon carbonation. At higher temperatures the reactions are accompanied by rearrangements and ring-opening.

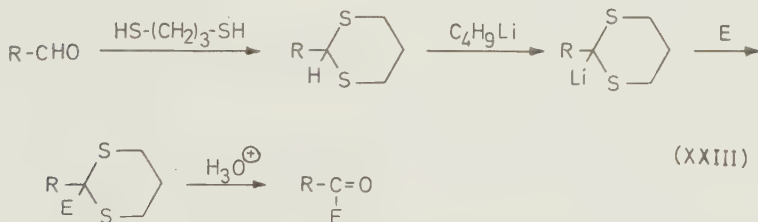
The fact that α -chloro- β -thienyllithia are stable at low temperatures has earlier been utilized e.g. in the preparation of fluorinated thiophenes in the reaction with perchloryl fluoride.⁷⁰

From the experiments with thienyllithia prepared from thiophenes containing mixed halogens, it can be concluded that many of them are stable in the range of -70° to -40° , the temperature interval for the normal halogen-metal exchanges; and thus are valuable intermediates for the introduction of different substituents. The exception to this are the α -bromo- β -thienyllithia; however here the accompanying rearrangements can sometimes be suppressed by working below -100° .

V.1 Introduction

Organic lithium compounds are strong nucleophiles. Therefore their use in synthetis would be greatly increased if they could be converted to electrophilic reagents, i.e., if the synthetic strategy of group equivalents with inverted reactivity, developed by Corey,⁷⁴ could be applied.

Corey and Seebach⁷⁵ have demonstrated the usefulness of this synthetic approach, in reversing the electrophilic properties of a carbonyl group by converting it to a 1,3-dithiane and metalating it with butyllithium, followed by the reaction with an electrophile (E) and hydrolysis to a carbonyl function.



Beringer et al. have successfully used diphenyliodonium salts for the arylation of different nucleophiles.³⁶ They also found that iodonium salts could, among other methods (cf. chapter II), be prepared from aryllithium and iodoso-dichlorides.^{39,42,43}

Therefore it was decided to investigate if iodonium salts containing at least one heterocyclic group could be used for the synthesis of thiophenes and then utilizing, in principle, the theories of reversed reactivity. If the efforts with thienyliodonium salts were successful, it would then be attractive to expand the investigations to furyl- and selenienyliodonium salts.

V.2 Unsymmetrical iodonium salts. Syntheses and reactions

The observation that iodonium salts are formed in the reaction between arylidioso dichloride and one equivalent of aryllithium³⁹ has been utilized in this work for the prepa-



ration of phenyl-thienyl-, mesityl-thienyl-, and p-anisyl-thienyliodonium salts. In this way phenyl-3-thienyliodonium chloride could be isolated in 73 % yield from the reaction of iodosobenzene dichloride⁷⁸ and 3-thienyllithium⁸ at -70° . Other phenyl-thienyliodonium chlorides could also be obtained in good yields by the same method (cf. Tables 5 and 6).

Theoretical calculations by Melander⁷⁹ indicated that thiophene should undergo nucleophilic displacement faster than benzene. Therefore it could be expected that path A in (XXV) should be favored over path B in the reaction between phenyl-3-thienyliodonium ion and a nucleophile (Nu:).

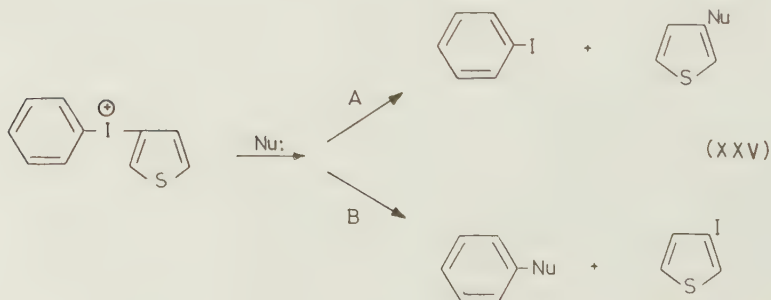


Table 5. Yields and melting points of phenyl-thienyliodonium chorides obtained in the reaction of thienyllithium derivatives with iodosobenzene dichloride.

Thienyllithium derivative	Iodonium chloride	Yield (%)	M.p. (°C) (dec.)
2-Thienyllithium ¹	Phenyl-2-thienyl-	51	226-227 ^{a,b}
3-Thienyllithium ²	Phenyl-3-thienyl-	73	249-251 ^b
4-Bromo-2-thienyl-lithium ^{3,4}	Phenyl-(4-bromo-2-thienyl)-	48	189-190 ^b

^aLit. value: 38 217-219°.

^bRecrystallized from water.

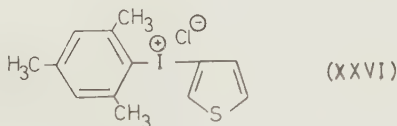
Table 6. Analytical data of phenyl-thienyliodonium chlorides obtained in the reaction of thienyllithium derivatives with iodobenzene dichloride.

Iodonium chloride	Elemental analyses			Molecular formula (Molecular weight)
	Found = F			
	Calculated = C			
	C	H	I	
Phenyl-2-thienyl-				
	F. 37.0	2.66	39.7	$C_{10}H_8ClIS$ (322.6)
Phenyl-3-thienyl-	C. 37.2	2.50	39.3	
Phenyl-(4-bromo-2-thienyl)-				
	F. 30.1	1.72	31.8	$C_{10}H_7BrClIS$ (401.5)
	C. 29.9	1.76	31.6	

However, when phenyl-3-thienyliodonium chloride was reacted with nitrite ion in dimethylformamide (DMF), it was found that the nucleophile predominantly attacked the phenyl ring. With methoxide ion in methanol the reaction took the same path; however, with this nucleophile, benzene and thiophene were also formed. This side-reaction must be ascribed to a radical reaction,⁸⁰ which will be discussed later (cf. V.6). Phenyl-2-thienyliodonium chloride behaved in the same manner as its 3-analogue. The vpc analyses of the reaction mixtures are given in Table 7 (columns C, D). The reactions were performed in closed ampoules to avoid the disappearance of volatile compounds and approximately 400 % excess of the nucleophile was used, and the total yields* were determined by addition of a known amount of an internal standard.

Beringer *et al.*³⁸ observed that phenyl-2-thienyliodonium trifluoroacetate and sodium sulphite in water led to the production of 2-iodothiophene and iodobenzene in a ratio of 1:2. This could be verified when the same reaction was performed with phenyl-2-thienyliodonium chloride. Thus it seems as if dianions behave somewhat different than monoanions, which predominantly gave rise to substitution on the phenyl ring.

As phenyl-thienyliodonium salts were not suitable for the synthesis of thiophenes, the interest was directed to mesityl-thienyliodonium salts. It was thought that the methyl groups in *e.g.* mesityl-3-thienyliodonium chloride should prevent the nucleophile to attack on the mesitylenecarbon. In addition to



* Since theoretically one mol of benzene derivatives and one mol of thiophene derivatives can be obtained from one mol of iodonium salt, the total percentage will be 200 %. The corresponding situation prevails of course also in the reaction of mesityl-thienyl and dithienyliodonium salts (cf. below).

Table 7. Total yields in the reaction of phenyl-thienyliodonium chlorides with sodium nitrite in N,N-dimethylformamide at 110° for 4.0 hours and sodium methoxide in methanol at 70° for 1.0 hour.

Iodonium chloride	Nucleophile (sodium salt)	Benzene	Thiophene	Iodo- benzene (%)	Iodo- thiophene (%)	Nitro- benzene (%)	Nitro- thiophene (%)
Phenyl-2-thienyl-	Nitrite	Trace	Trace	10	93 ^a	97	Trace
Phenyl-3-thienyl-	Nitrite	Trace	Trace	17	84 ^b	82	19 ^c
						Methoxy- benzene (%)	Methoxy- thiophene (%)
Phenyl-2-thienyl-	Methoxide	17	14	14	71 ^a	56	-
Phenyl-3-thienyl-	Methoxide	19	20	24	79 ^b	45	2 ^d

^a 2-Iodothiophene.

^b 3-Iodothiophene.

^c 3-Nitrothiophene.

^d 3-Methoxythiophene.

this steric effect methyl groups are somewhat electron-releasing, which should lead to higher electron density at the carbon bond to iodine in the mesityl ring, which also should favor nucleophilic attack on the thiophene part of the salt.

The preparation of iodosomesitylene dichloride was accompanied by several complications. Chloroform is normally used as the solvent for the chlorination of iodobenzene; however, if this solvent is used in the same reaction with iodosesitylene, chlorination of the ring could, as noted earlier,⁸¹ be observed. This was easily studied by NMR. It has been reported that acetic acid is a better solvent than chloroform for the chlorination of iodosesitylene.⁸¹ These results, however, could not be reproduced, since it could be observed that this solvent likewise promotes rearrangement. In contrast to these two solvents, hexane was found to be an excellent solvent, and the iodosomesitylene dichloride obtained in this case was stable for several days if stored at about -20° .

Iodosomesitylene dichloride and thienyllithium gave, in the same way as iodosobenzene dichloride, good yields of mesityl-thienyliodonium salts (Tables 8 and 9).

Somewhat surprisingly, it was found that the introduction of a mesityl, instead of a phenyl ring, did not have any effect on the direction of the reaction; the products consisted mainly of iodothiophene and a substituted mesitylene. If methoxide ion was used as a nucleophile, the formation of mesitylene and thiophene was observed. In Table 10 the total yields in the reactions between mesityl-thienyliodonium chlorides and nucleophiles are given.

As steric effects and weak electron-donating groups did not change the reaction path, another possibility was that a strongly electron-donating group para to the carbon-iodine bond in the benzene ring would favor attack on the heterocycle. p-Iodoanisole²³ could be chlorinated in hexane at -60° . When the p-iodosoanisyl dichloride was suction dried on glass filter to remove excess chlorine, the iodoso dichloride was stable for only a few minutes; a vigorous reaction then occurred in connection with the rearrangement of the iodoso dichloride to chlorinated p-iodoanisoles with the liberation of hydrogen chloride. If, however, p-iodosoanisyl dichloride was filtered

Table 8. Yields and melting points of mesityl-thienyliodonium chlorides obtained in the reaction of thienyllithium derivatives with iodosomethylene-dichloride.

Thienyllithium derivative	Iodonium chloride	Yield (%)	M.p. (°C) (dec.)
2-Thienyllithium ¹	Mesityl-2-thienyl-	40 ^a	165-166
3-Thienyllithium ⁸	Mesityl-3-thienyl-	63 ^a	184-185
2-Chloro-3-thienyl-lithium	Mesityl-(2-chloro-3-thienyl)-	53 ^a	130-131
4-Bromo-2-thienyl-lithium ⁵⁴	Mesityl-(4-bromo-2-thienyl)-	39 ^a	160-162

^aRecrystallized from water.

Table 9. Analytical data of mesityl-3-thienyliodonium chlorides obtained in the reaction of thienyllithium derivatives with iodosomesitylene dichloride.

Iodonium chloride	Elemental analyses			Molecular formula (Molecular weight)
	Found = F			
	Calculated = C			
	C	H	II	
Mesityl-2-thienyl-	F. 42.9	3.84	34.5	$C_{13}H_{14}ClIS$ (364.7)
	C. 42.8	3.87	34.8	
Mesityl-3-thienyl-	F. 42.2	3.74	34.2	$C_{13}H_{14}ClIS$ (364.7)
	C. 42.8	3.87	34.8	
Mesityl-(2-chloro-3-thienyl)-	F. 38.9	3.15	32.0	$C_{13}H_{13}Cl_2IS$ (399.1)
	C. 39.1	3.28	31.8	
Mesityl-(4-bromo-2-thienyl)-	F. 34.9	2.85	28.8	$C_{13}H_{13}BrClIS$ (443.6)
	C. 35.5	2.95	28.6	

Table 10. Total yields in the reactions of mesityl-2-thienyliodonium chloride with sodium nitrite in N,N-dimethylformamide at 110° for 4.0 hours and sodium methoxide in methanol at 70° for 1.0 hour.

Iodonium chloride	Nucleophile (sodium salt)	Mesitylene (%)	Thiophene (%)	Iodo- mesitylene (%)	Iodo- thiophene (%)	Nitro- mesitylene (%)	Nitro- thiophene (%)
Mesityl-2-thienyl-	Nitrite	-	Trace	23	86 ^a	88	-
Mesityl-3-thienyl-	Nitrite	-	Trace	1	99 ^b	100	-
						Methoxy- mesitylene (%)	Methoxy thiophene (%)
Mesityl-2-thienyl-	Methoxide	53	13	37	64 ^a	17 ^{d,e}	-
Mesityl-3-thienyl-	Methoxide	50	12	23	84 ^b	30 ^{d,e}	Trace ^c

^a 2-Iodothiophene.

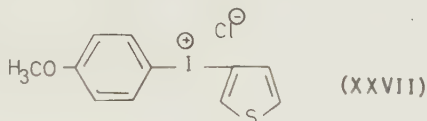
^b 3-Iodothiophene.

^c 3-Methoxythiophene.

^d The sensitivity factor of methoxymesitylene was set equal to that of iodomesitylene.

^e Could not be separated from a small contamination at the gas chromatographic analyses.

quickly to remove the major portion of the chlorine and was then added to an already prepared 3-thienyllithium⁸ solution, p-anisyl-3-thienyliodonium chloride was obtained in 5 % yield.



The low yield and the fact that a quite pure salt was not obtained, not even after recrystallization, can be explained since not all the chlorine gas could be removed from the iodoso dichloride. The remainder of chlorine reacts with thienyllithium, lowering the yield of iodonium salt; additionally chlorination of one or both of the rings can occur, making the isolation of a pure salt difficult.

Even when p-anisyl-3-thienyliodonium chloride was not obtained pure, it was reacted with nitrite ion, showing a product distribution consisting of p-iodoanisole (45 %), 3-iodothiophene (9 %), p-nitroanisole (39 %) and 3-nitrothiophene (7 %). (Here the sensitivity factor of p-nitroanisole was set equal to that of p-iodoanisole.) This indicates that a p-methoxy group has a small effect on directioning the path of the reaction; this effect is, however, too small to utilize p-anisyl-thienyliodonium salts for the synthesis of thiophenes. Concerning the relative ratios of the products, the product distribution is somewhat surprising since it could be expected that 3-nitrothiophene and p-iodoanisole as well as 3-iodothiophene and p-nitroanisole should be formed in equal quantities. The explanation can here lie in a complex radical reaction eventually combined with tar formation.

While this work was in progress, an investigation on the pyrolysis of phenyl-2-thienyl- and substituted phenyl-2-thienyliodonium chlorides and bromides was published.^{82,83} In accordance with the reactions with nitrite and methoxide ion, it was also found^{82,83} that the obtained products could to the greatest extent be derived from substitution on the benzenic ring. If solvents such as DMF or dioxane were used, the result

was the same. The introduction of chlorine, a methyl or a methoxy group para to iodine in the phenyl ring directioned the substitution partly into path A; path B was, however, still preferred (cf. XXV).

These results could be confirmed when phenyl-3-thienyl-iodonium chloride was pyrolyzed in a glass tube. It was found that chlorobenzene, 3-chlorothiophene, iodobenzene, and 3-iodothiophene were formed in a ratio of about 4:1:1:4. This result deviates somewhat from that obtained with phenyl-2-thienyl-iodonium chloride, since with this latter salt substitution occurred only on the phenyl ring.⁸² This can, of course, be a reflection in the difference in reactivity of 2- and 3-thienyl-iodonium salts.

The results from the reactions of unsymmetrical iodonium salts with nucleophiles indicate that another reaction mechanism other than that connected with a pure S_N2 mechanism prevails. This possibility will be penetrated later (cf. V.6).

To check if phenyl-furyliodonium salts would behave in the same way as their thiophene analogues, efforts were made to prepare phenyl-[2-(2-(1,3-dioxolanyl))-3-furyl]iodonium chloride from iodosobenzene dichloride⁷⁸ and 2-(3-lithio-2-furyl)-1,3-dioxolane.²⁷ The iodonium chloride obtained from these reagents was somewhat unstable at room temperature when isolated and had to be used directly after filtering. When this salt was reacted with sodium nitrite in DMF, it was found that substitution occurred exclusively on the benzene ring.

If trans-chlorovinyl-3-thienyliodonium chloride could be prepared from trans-chlorovinylidoso dichloride⁴² and one equivalent of 3-thienyllithium,⁹ treatment with one equivalent of a second heterocyclic lithium derivative should give unsymmetrical iodonium chlorides containing mixed heterocycles. An effort to prepare trans-chlorovinyl-3-thienyliodonium chloride using the above method failed, however, in that di-(3-thienyl)-iodonium chloride was obtained instead of the desired unsymmetrical iodonium salt. This indicates that the reaction of 3-thienyllithium with the intermediate trans-chlorovinyl-3-thienyliodonium chloride is a more favorable process than the reaction of 3-thienyllithium with trans-chlorovinylidoso dichloride.

An additional intention was to synthesize (1-methyl-4-pyrazoyl)-3-thienyliodonium chloride from 3-thienyllithium⁸ and 1-methyl-4-iodosopyrazol dichloride. The hope was that in such an unsymmetrical iodonium salt the nucleophile would prefer the thiophene part of the salt. According to NMR, the chlorination of 4-iodo-1-methylpyrazole⁸⁴ gave, however, a mixture of products. The product mixture probably consisted of different ring-chlorinated iodoso dichlorides eventually mixed with only ring-chlorinated 4-iodo-1-methylpyrazoles. Treatment of the isolated yellow, viscous product with 3-thienyllithium⁸ at -70° gave no iodonium salt.

As unsymmetrical iodonium salts were not suitable for the synthesis of heterocyclic compounds, it was decided to expand the investigations to symmetrical iodonium salts.

V.3 Symmetrical dithienyliodonium salts. Syntheses and reactions.

Berlinger and Nathan found that symmetrical diaryliodonium salts could be prepared from trans-chlorovinylidoso dichloride and two equivalents of aryllithium;⁴² by this method, they also obtained di-(2-thienyl)- and di-(2-furyl)iodonium iodide.⁴³ This



synthetic procedure has been used for the preparation of dithienyliodonium chlorides, which could be isolated in good yields (cf. Tables 11 and 12). In connection with the syntheses of these salts, it was found that usually a somewhat higher yield of iodonium chlorides was obtained by adding the thienyllithium solution to the trans-chlorovinylidoso dichloride in toluene, verifying earlier observations.⁴² This technique was not extended to the unsymmetrical iodonium salts, because they were, as reported above, not suitable for the preparation of heterocyclic compounds. Additionally, unsymmetrical iodonium salts could be isolated in good yields even if the most effective method was not utilized; it is of course possible

that the yields can be somewhat improved if the reverse addition order is used.

When the crude symmetrical dithienyliodonium chlorides listed in Table 11 were reacted with sodium nitrite in DMF, 30-50 % yields (with one exception) of pure isomer-free nitrothiophenes were obtained.⁸⁷ With water as solvent, the yields were lower due to tar formation.

In Tables 13-15, the yields and analytical data of the obtained nitrothiophenes are given. In no case were products from the attack of oxygen on the thiophene ring observed. This does, of course, not exclude this possibility, since it is possible that the formed thienyl nitrites are unstable at the reaction temperature of 110°.

In addition to the nitrothiophenes in Table 13, prepared directly from iodonium chlorides, 2-(4-nitro-3-thienyl)-1,3-dioxolane gave upon hydrolysis 3-formyl-4-nitrothiophene in 100 % yield. Several attempts to prepare pure 4-bromo-2-nitrothiophene via the same method, from di-(4-bromo-2-thienyl)-iodonium chloride was not successful. Only a low yield (5-10 %) of the desired nitrothiophene could be isolated and this product was not isomer-free. The presence of an isomer originates from the fact that 2,4-dibromothiophene,⁵⁴ the starting material for di-(4-bromo-2-thienyl)iodonium chloride, contains approximately 5 % of 2,3-dibromothiophene, (easily revealed by vpc (column A or C)). The 2,3-dibromothiophene is formed since the halogen-metal exchange reaction between 2,3,5-tribromothiophene and alkyl lithium does not exclusively go in the 2-position. The illustrated method can be considered to be a convenient route to several substituted nitrothiophenes, not available through direct electrophilic substitution. Other known methods for the preparation of pure 2-nitrothiophene^{88a} and 3-nitrothiophene⁸⁹ suffer from the disadvantage that electrophilic nitration reactions lack in selectivity⁹⁰ and the following separation of the isomers is a rather tedious procedure.^{88a} The advantages of the iodonium salt method for preparation of isomer-free nitrothiophenes are even more evident in regard to the difficulties demonstrated in a paper,^{88b} totally devoted to the problem of separation of 2- and 3-nitrothiophene.

Table 11. Yields and melting points of dithienyliodonium chlorides obtained in the reaction of thienyllithium derivatives with trans-chlorovinylidioso dichloride.

Thienyllithium derivative	Iodonium chloride	Yield (%)	Recryst. from	M.p. (°C) (dec.)
2-Thienyllithium ¹	Di-(2-thienyl)-	69	Water	188-190 ^a
3-Thienyllithium ⁸	Di-(3-thienyl)-	84	Water	239-240
4-Bromo-3-thienyl-lithium ⁸⁵	Di-(4-bromo-3-thienyl)-	66	MeOH	206-208
4-Bromo-2-thienyl-lithium ⁵⁴	Di-(4-bromo-2-thienyl)-	42	MeOH	137-138
4-Methyl-3-thienyllithium ⁸⁵	Di-(4-methyl-3-thienyl)-	58	Water	223-227
2-(4-Lithio-3-thienyl)-1,3-dioxolane ⁸⁶	Di-[4-(2-(1,3-dioxolanyl))-3-thienyl]-	52	MeOH	176-178
4-Methylthio-3-thienyllithium ⁶³	Di-(4-methylthio-3-thienyl)-	61	Water	183-185
2-Chloro-3-thienyl-lithium	Di-(2-chloro-3-thienyl)-	71	Water	195-197

Table 11. (contd.)

Thienyllithium derivative	Iodonium chloride	Yield (%)	Recryst. from	M.p. (°C) (dec.)
2-Chloro-4-thienyl- lithium ⁷⁰	Di-(2-chloro-4- thienyl)-	65	Water	125-127
4-Chloro-3-thienyl- lithium	Di-(4-chloro-3- thienyl)-	64	Water	156-157

^aLit. value: ³⁸ 229-230°.

Table 12. Analytical data of dithienyliodonium chlorides obtained in the reaction of thienyllithium derivatives with trans-chlorovinylidioso dichloride.

Iodonium chloride	Elemental analyses			Molecular formula (Molecular weight)
	Found = F			
	Calculated = C			
	C	H	I	
Di-(2-thienyl)-				$C_8H_6ClIS_2$ (328.6)
	F. 29.3	1.76	38.9	
Di-(3-thienyl)-				$C_8H_6ClIS_2$ (328.6)
	C. 29.2	1.84	38.6	
Di-(4-bromo-3-thienyl)-				$C_8H_4Br_2ClIS_2$ (486.4)
	F. 20.2	1.09	26.2	
	C. 19.7	0.83	26.1	
Di-(4-bromo-2-thienyl)-				$C_8H_4Br_2ClIS_2$ (486.4)
	F. 20.0	0.87	26.2	
	C. 19.7	0.83	26.1	
Di-(4-methyl-3-thienyl)-				$C_{10}H_{10}ClIS_2$ (356.7)
	F. 33.2	2.64	35.7	
	C. 33.7	2.83	35.6	

Table 12. (contd.)

Iodonium chloride	Elemental analyses			Molecular formula (Molecular weight)
	Found = F			
	Calculated = C			
	C	H	I	
Di-[4-(2-(1,3-dioxolanyl))-3-thienyl]-	F. 35.3	2.97	27.0	$C_{14}H_{14}ClIO_4S_2$ (472.7)
	C. 35.6	2.99	26.8	
Di-(4-methylthio-3-thienyl)-	F. 28.0	2.47	30.2	$C_{10}H_{10}ClIS_4$ (420.8)
	C. 28.5	2.40	30.2	
Di-(2-chloro-3-thienyl)-	F. 24.4	1.07	32.2	$C_8H_4Cl_3IS_2$ (397.5)
	C. 24.2	1.01	31.9	
Di-(2-chloro-4-thienyl)-	F. 24.3	1.00	32.3	$C_8H_4Cl_3IS_2$ (397.5)
	C. 24.2	1.01	31.9	
Di-(4-chloro-3-thienyl)-	F. 24.4	1.04	31.8	$C_8H_4Cl_3IS_2$ (397.5)
	C. 24.2	1.01	31.9	

Table 13. Yields of nitrothiophenes obtained in the reaction of dithienyl-iodonium chlorides with sodium nitrite in N,N-dimethylformamide.

Iodonium chloride	Nitrothiophene	Yield (%)
Di-(2-thienyl)-	2-Nitrothiophene	31
Di-(3-thienyl)-	3-Nitrothiophene	52
Di-(4-bromo-3-thienyl)-	3-Bromo-4-nitro-thiophene	58
Di-(4-methyl-3-thienyl)-	3-Methyl-4-nitro-thiophene	42
Di-[4-(2-(1,3-dioxo-1anyl))-3-thienyl]-	2-(4-Nitro-3-thienyl)-1,3-dioxolane	50
Di-(4-bromo-2-thienyl)-	4-Bromo-2-nitro-thiophene ^a	<10
	3-Formyl-4-nitro-thiophene ^b	100

^a Contaminated by about 5 % of 3-bromo-2-nitrothiophene.

^b Prepared from 2-(4-nitro-3-thienyl)-1,3-dioxolane.

Table 14. Analytical data of nitrothiophenes obtained in the reaction of dithienyliodonium chlorides with sodium nitrite in N,N-dimethylformamide.

Nitrothiophene	M.p. (°C)	M.p. (°C) Lit. value	Elemental analyses			Molecular formula (Molecular weight)
			Found = F			
			Calculated = C			
			C	H	S	
2-Nitrothiophene	40.4-40.7	40.5-41.5 ^{88a}				
3-Nitrothiophene	75.7-75.9	75-75.5 ⁸⁹				
3-Bromo-4-nitro- thiophene	77.8-78.1	79-80 ⁹¹				
3-Methyl-4-nitro- thiophene	44.0-44.4	-	F. 42.3	3.69	22.7	C ₅ H ₅ NO ₂ S (143.2)
			C. 41.9	3.52	22.4	
2-(4-Nitro-3-thienyl)- 1,3-dioxolane	67.5-68.0		F. 42.1	3.43	16.0	C ₇ H ₇ NO ₄ S (201.2)
			C. 41.8	3.51	15.9	
4-Bromo-2-nitro- thiophene ^a	43-44	46-47 ⁹¹				
3-Formyl-4-nitro- thiophene ^b	71.2-71.6	-	F. 38.4	1.98	20.3	C ₅ H ₃ NO ₃ S (157.1)
			C. 38.2	1.91	20.4	

^a Contaminated by about 5 % of 3-bromo-2-nitrothiophenes. ^b Prepared from 2-(4-nitro-3-thienyl)-1,3-dioxolane.

Table 15. NMR data of nitrothiophenes prepared from dithienyliodonium chlorides.

Nitrothiophene	NMR data (CDCl ₃)
3-Bromo-4-nitro-thiophene	$\delta_2 = 7.42$ ppm, $\delta_5 = 8.36$ ppm, $J_{2,5} = 3.8$ Hz
3-Methyl-4-nitro-thiophene	$\delta_2 = 7.02$ ppm, $\delta_5 = 8.30$ ppm, δ_{CH_3} $J_{2-CH_3} = 1.0$ Hz, $J_{2,5} = 3.7$ Hz
2-(4-Nitro-3-thienyl)-1,3-dioxolane	$\delta_2 = 7.55$ ppm, $\delta_5 = 8.31$ ppm, δ_{CH} = 6.36 ppm, $\delta_{CH_2-CH_2} = 4.05$ ppm, $J_{2-CH} = 0.8$ Hz, $J_{2,5} = 3.8$ Hz
4-Bromo-2-nitro-thiophene	$\delta_3 = 7.28$ ppm, $\delta_5 = 8.04$ ppm, $J_{3,5} = 1.8$ Hz
3-Formyl-4-nitro-thiophene ^a	$\delta_2 = 8.20$ ppm, $\delta_5 = 8.42$ ppm, $\delta_{CHO} = 10.37$ ppm, $J_{2,5} = 3.7$ Hz

^aPrepared from 2-(4-nitro-3-thienyl)-1,3-dioxolane.

The progress with the preparation of nitrothiophenes indicated that also other substituents should be easily introduced.

The attack of nucleophiles on iodonium salts seems, however, to be more complex than expected. With some nucleophiles the reaction between dithienyliodonium salts and nucleophiles goes smoothly, but with others the desired compounds are not obtained. With nucleophiles such as alkoxides, cyanide, fluoride ion and the anion of diethyl malonate, the products consisted of iodothiophene accompanied in most cases by thiophene and tar formation. The amount of thiophene formed, which must be ascribed to a radical reaction (cf. below), depended both on the nucleophile and the solvent used. Even amines, such as piperidine, gave no thienylpiperidine but, instead, iodothiophene and thiophene. With some nucleophiles which did not yield substituted thiophenes, it was found that the addition of either 1,1-diphenylethylene or copper salts changed the reaction path in a way that the desired thiophenes were obtained. The copper-catalyzed reactions will be treated in a following part of this chapter, where the influence of the presence of 1,1-diphenylethylene will also be taken up.

Beringer *et al.* found that ethyl sodiooxalacetate and diphenyliodonium salts gave phenylmalonates.⁴⁴ They also tried to synthesize phenylmalonates from iodonium salts and diethyl malonate anion, but, in general, the yields were low due to side reactions.⁸⁰

It would be an improvement in the syntheses of fluorinated thiophenes and even diethyl malonates, if fluorine or a diethyl malonate group could be introduced via the iodonium salts since fluorothiophenes are generally prepared from thienyllithium and the hazardous perchlorylfluoride,⁷⁰ and the route to diethyl thienylmalonates is rather inconvenient.⁹²

Fluoride and diethyl malonate ion resisted all attempts to give substituted thiophenes. The reaction between fluoride ion and di-(3-thienyl)iodonium tetrafluoroborate, prepared by treatment of di-(3-thienyl)iodonium chloride with a silver tetrafluoroborate solution, was tried using sodium and potassium fluoride both in the presence and absence of copper sulphate in solvents such as DMF, DMSO, nitrobenzene, acetonitrile, and water. Attempts to pyrolyze di-(3-thienyl)iodonium fluoride, prepared by

methathesis in the corresponding way as that described for diphenyliodonium fluoride,⁹³ gave only 3-iodothiophene and polymeric products, as in the reactions performed in solution. The reaction of di-(3-thienyl)iodonium tetrafluoroborate and potassium fluoride in the presence of disilverfluoride⁹⁴ failed both in DMSO and in nitrobenzene. Sodium diethyl malonate was in the same way allowed to react with di-(3-thienyl)iodonium chloride in different solvents such as water, DMF, liquid ammonia and methanol. The only products were 3-iodothiophene and thiophene, together with coupling products of the diethyl malonate anion.

The addition of copper(I) or copper(II) salts did not catalyze the formation of diethyl thienylmalonate. Ethyl sodium-oxalacetate behaved in the same way as the malonate anion.

In addition to the nitrite ion, there were other nucleophiles which easily gave substituted thiophenes, even without catalysts. When di-(3-thienyl)iodonium chloride was reacted with sodium thiocyanate in DMF, 3-thiocyanothiophene could be isolated in 43 % yield. Other dithienyliodonium chlorides gave in the same way substituted thiocyanothiophenes (cf. Tables 16-18). In addition to those thiocyanothiophenes listed in Table 16, qualitative experiments showed that also 3-chloro-4-thiocyanothiophene can be prepared from di-(3-chloro-4-thienyl)iodonium chloride. The yields of thiocyanothiophenes from iodonium salts indicate that this method is superior to that using cyanogen bromide and the sodium salt of 3-thiophenethiol,⁵¹ where dithienyl disulphide is the main product.

In connection with the preparation of thiocyanothiophenes, it was investigated whether isothiocyanothiophenes were also formed. By combined vpc-mass spectrometry it could be shown that isothiocyanothiophenes were probably produced, but that their concentrations in the reaction mixtures were, in general, less than 3 % that of the thiocyanothiophenes. The indication for formation of e.g. 3-isothiocyanothiophene from the reaction of di-(3-thienyl)iodonium chloride and sodium thiocyanate was that the mass spectra of 3-thiocyanothiophene and the other product were quite similar. Both products gave the same molecular ions ($M^+ = 141, 142, 143$), but $m/e = 125$ which was of high abundance in the spectrum of the assumed 3-isothiocyano-

Table 16. Yields of thiocyanothiophenes obtained in the reaction of di-thienyliodonium chlorides with sodium thiocyanate in N,N-dimethylformamide.

Iodonium chloride	Thiocyanothiophene	Yield (%)
Di-(3-thienyl)-	3-Thiocyanothiophene	43
Di-(2-chloro-3-thienyl)-	2-Chloro-3-thiocyano-	44
Di-(4-methylthio-3-thienyl)-	3-Methylthio-4-thio- cyanothiophene	23
Di-(4-bromo-3-thienyl)-	3-Bromo-4-thiocyano- thiophene	37
Di-(2-chloro-4-thienyl)-	2-Chloro-4-thiocyano- thiophene	17

Table 17. Analytical data of thiocyanathiophenes obtained in the reaction of dithienyliodonium chloride with sodium thiocyanate in N,N-dimethylformamide.

Thiocyanathiophene	B.p. (°C/mm Hg)	M.p. (°C)	Elemental analyses				Molecular formula (Molecular weight)
			Found = F Calculated = C				
			C	H	N	S	
3-Thiocyanathiophene	107-110/11 ^a						
2-Chloro-3-thiocyano- thiophene	120-126/12		F. 34.1	1.13	7.76	-	C ₅ H ₂ ClNS ₂ (175.6)
	120-126/12		C. 34.2	1.15	7.98	-	
3-Methyl-4-thio- cyanothiophene	164-168/11	47.8-48.4	F. 38.3	2.71	-	51.3	C ₆ H ₅ NS ₃ (187.3)
			C. 38.5	2.69	-	51.4	
3-Bromo-4-thiocyano- thiophene	150-153/12	54.6-56.0	F. 27.2	1.00	-	29.2	C ₅ H ₂ BrNS ₂ (220.1)
			C. 27.3	0.91	-	29.1	
2-Chloro-4-thiocyano- thiophene ^b	121-124/11		F. 33.2	1.13	7.54	-	C ₅ H ₂ ClNS ₂ (175.6)
			C. 34.2	1.15	8.02	-	

^aLit. value: 51 114-115°/15.

^bNot quite pure after preparative gas chromatography.

Table 18. NMR data of thiocyanothiophenes prepared from dithienyliodonium chlorides.

Thiocyanothiophene	NMR data (CDCl ₃)
2-Chloro-3-thiocyanothiophene	$\delta_4 = 7.08$ ppm and $\delta_5 = 7.25$ ppm, $J_{4,5} = 5.7$ Hz
2-Chloro-4-thiocyanothiophene	$\delta_3 = 7.03$ ppm and $\delta_5 = 7.37$ ppm, $J_{3,5} = 1.7$ Hz
3-Methylthio-4-thiocyanothiophene	$\delta_2 = 7.16$ ppm and $\delta_5 = 7.68$ ppm, $\delta_{CH_3} = 2.47$ ppm, $J_{2,5} = 3.2$ Hz
3-Bromo-4-thiocyanothiophene	$\delta_2 = 7.43$ ppm and $\delta_5 = 7.70$ ppm, $J_{2,5} = 3.4$ Hz

thiophene was absent in the fragmentation pattern of 3-thiocyanothiophene. Other fragments showed only small deviations. 3-Thiocyanothiophene had a longer retention time than the other product in the gas chromatogram (column: C). All of the isolated 3-thiocyanothiophenes show strong absorption at approximately 2165 cm^{-1} in their IR spectra, as do 3-thiocyanofuran and 3-thiocyanoselenophene (cf. V.4). This IR absorption is characteristic of aromatic thiocyno compounds.

Di-3-thienyliodonium chloride and sodium phenolate in water gave 3-thienyl-phenyl ether in 23 % yield. If sodium phenoxide in methanol was used, the yield of 3-thienyl-phenyl ether was very low. Instead, considerable amounts of thiophene were formed.

In connection with this, efforts were made to prepare 3-thienyl-phenyl ether by reacting 3-bromothiophene⁹ with sodium phenolate in methanol in the presence of copper(II) oxide. The purpose was to see if the copper-catalyzed reaction between 3-bromothiophene and sodium methoxide in methanol, which gives 3-methoxythiophene,⁹⁵ could be extended to thienyl-phenyl ethers. However, after reflux for 96 hours only 2 % of the starting material was converted to 3-thienyl-phenyl ether. If DMF was used as solvent, no 3-thienyl-phenyl ether could be detected. 3-Iodothiophene⁵¹ in methanol gave under the same conditions only traces of 3-thienyl-phenyl ether.

Diphenyl ethers have earlier been prepared from diphenyliodonium salts and sodium phenolate.^{44,96} The use of dithienyliodonium salts has now extended this synthetic method to thienyl-phenyl ethers, the synthesis of which does not seem to be reported earlier in the literature.

From 3-bromothiophene⁹ and sodium thiophenolate, 3-thienyl-phenyl sulphide could be obtained in 75 % yield.⁹⁷ Di-(3-thienyl)iodonium chloride and sodium thiophenolate likewise gave 3-thienyl-phenyl sulphide, but only in 26 % yield. In this latter reaction, considerable amounts of diphenyl disulphide was formed. Another route to 3-thienyl-phenyl sulphide is the reaction between 3-thienyllithium and phenylthiocyanate, where the yield is reported to be 44 %.⁹⁸ Thus, the route *via* iodonium salts to thienyl-phenyl sulphides seems to be inferior to the other known methods, but can, of course, be an alternative in some special cases.

Di-3-thienyliodonium chloride and piperidyl anion in acetonitrile gave 3-iodothiophene together with some products, which could not be identified with accuracy. No 3-piperidinothiophene could be detected in the reaction mixture. If nitrobenzene was used as solvent in the reaction between di-(3-thienyl)iodonium chloride and piperidyl anion the products, according to vpc-mass spectrometry, consisted of thiophene, 3-iodothiophene, aniline and azoxybenzene. The latter two products must have their origin in reduction reactions of nitrobenzene.

The anion of acetonitrile gave, with di-(3-thienyl)iodonium chloride in acetonitrile, no substituted thiophene in addition to 3-iodothiophene. When copper sulphate was added, combined vpc-mass spectrometry indicated that two derivatives of thiophene had been formed. The product with the shorter retention time in the gas chromatogram (column E) did not show any intense molecular ion, and had $m/e = 82$ as the most abundant fragment, with $m/e = 55, 57, 67, 83,$ and 97 also being in high abundance. It is possible that this product is N-(3-thienyl)-keteneimine, if it is assumed that the $m/e = 97$ peak has its origin in the elimination of the $-C=CH_2$ fragment leading to $M^+ - 26 = m/e = 97$. The expected molecular ion $M^+ = 123$ was of low intensity. The other product, having longer retention time, showed a molecular ion of $M^+ = 205$ as the most abundant ion. Other fragments of high intensity were: $m/e = 57, 66, 71, 78, 81, 82, 83, 85, 96, 98, 102, 107, 119, 120, 131, 136, 149, 161, 171, 172, 173, 190, 204,$ and 206 . The structure of this latter product could, however, not be deduced with certainty, but possibly has 1,1-di-(3-thienyl)acetonitrile been formed.

As indicated above, the addition of copper salts or 1,1-diphenylethylene strongly influences the reaction between iodonium salts and nucleophiles and extends the number of useful nucleophiles. These latter reactions will be discussed in a following part (V:5) of this chapter.

V.4 Symmetrical difuryl- and diselenienyliodonium salts. Syntheses and reactions

Since it had been possible to synthesize several substi-

tuted thiophenes from symmetrical dithienyliodonium salts, it was of interest to see if also the corresponding furyl- and selenienyliodonium salts would in the same way be useful for the preparation of furans and selenophenes.

The simple nitrofurans and nitroselenophenes are, with the exception of 2-nitrofuran, difficult to obtain in isomer-free form. 2-Nitrofuran is readily prepared by nitration of furan;⁹⁹⁻¹⁰¹ 3-nitrofuran is reported only once in the literature.¹⁰² 3-Nitrofuran was prepared in very low yield in a complex way starting from 2-methyl-5-formylfuran, via 2-methyl-5-furancarboxylic acid, 3-nitro-2-methyl-5-furancarboxylic acid, 2-methyl-3-nitrofuran, and 3-nitro-2-furancarboxylic acid. The synthesis of 3-nitrofurans is limited by the high reactivity of the α -positions in furan relative to the β -positions, often preventing electrophilic substitutions from occurring in the β -position without the accompanying exchange of substituents in the α -positions.

The preparation of pure 2- and 3-nitroselenophene is likewise complicated by formation of unwanted isomers. Nitration of selenophene leads to a mixture of 2- and 3-nitroselenophene, which are difficult to separate. A preparation of 2-nitroselenophene described by Umezawa¹⁰³ was shown by Yur'ev et al.¹⁰⁴ to be a mixture of 3-nitroselenophene (70 %) and 2-nitroselenophene (30 %). Yur'ev and coworkers also succeeded in increasing the total yield of mononitro isomers from 15 % to 25 %.¹⁰⁵ They could not, however, separate the isomers, and prepared pure 2-nitroselenophene by decarboxylation of 5-nitro-2-selenophene-carboxylic acid.¹⁰⁴

Paulmier et al. used 2- and 3-nitroselenophene for the synthesis of selenolo[2,3-b]- and selenolo[3,2-b]pyridine.¹⁰⁶ They claimed (without experimental details) that by nitration at -40° , a mixture of only 2- and 3-nitroselenophene (7:3) was obtained in 30 % yield. Both isomers were separated by repeated chromatography on Florisil. 3-Nitroselenophene has also been obtained indirectly by nitration of 2-acetylselenophene¹⁰⁷ and 2-formylselenophene¹⁰⁴ followed by oxidation and decarboxylation and from nitration of 2-selenophenesulphonyl chloride followed by desulphonation.¹⁰⁸ In all these latter cases, it was necessary to separate the 4-nitro-2-selenophene derivatives from the

5-nitro-2-selenophene derivatives formed in the nitration. A further complication was the elimination of substituents, leading to 2,4-dinitroselenophene.^{104,107}

Using the same method as for the preparation of nitrothiophenes (cf. V.3), both nitrofurans and nitroselenophenes could be prepared.¹⁰⁹ As by-products the corresponding iodo compounds were obtained.

Berlinger *et al.* reported that di-(2-furyl)iodonium chloride could be obtained in 86 % yield from the reaction between 2-furyllithium and *trans*-chlorovinylidioso dichloride.⁴³ This high yield could not be repeated, in spite of several attempts and modifications, when trying to synthesize both di-(2-furyl)-iodonium chloride and the iodide. Only a 35 % yield of di-(2-furyl)iodonium chloride was obtained. When this salt was reacted with sodium nitrite in DMF, 2-nitrofuran was isolated in 35 % yield.

3-Furyllithium,³² prepared by halogen-metal exchange at -70° , and *trans*-chlorovinylidioso dichloride gave di-(3-furyl)-iodonium chloride in 54 % yield. In this case the reaction with nitrite ion in water or DMF yielded only furan and 3-iodofuran. The prevailing side-reaction could not be suppressed by addition of copper salts. Addition of 1,1-diphenylethylene resulted in 3-nitrofuran appearing in the reaction mixture, but still side-reactions were dominant. However, it was found that in both nitrobenzene and 1,3-dinitrobenzene, the arylation of the nitrite ion proceeded normally. The latter solvent is to be preferred due to more convenient separation of the 3-nitrofuran from the solvent, because of the close boiling points of nitrobenzene and 3-nitrofuran. In this way a 31 % yield of 3-nitrofuran was obtained.

2-Thiocyanofuran is conveniently prepared from furan and thiocyanogen in the presence of AlCl_3 .³² In contrast, the reaction of 3-chloromercuryfuran with thiocyanogen gave in low yield a product consisting of 2-thiocyanofuran (80 %) and 3-thiocyanofuran (20 %).³² The isolation of 3-thiocyanofuran from the reaction of di-(3-furyl)iodonium chloride and sodium thiocyanate was also combined with difficulties. In DMF, 3-thiocyanofuran was formed in low yield, but after work-up and following distillation it had a great tendency to decompose.

The best solvent was found to be DMF. After the reaction was finished most of the DMF was roughly distilled off and the remainder carefully stillled. The fractions collected contained 3-thiocyanofuran together with some DMF. By preparative gas chromatography pure 3-thiocyanofuran could be isolated in low yield. Dioxane, glycerol, sulpholane, formamide, p-nitrotoluene, nitromesitylene, quinoline, nitromethane, hexametapole, methanol, acetonitrile, and water were also tried as solvents, but in none of these was the yield of 3-thiocyanofuran improved compared to DMF. In any case, these efforts led to the first reported NMR spectrum of pure 3-thiocyanofuran.

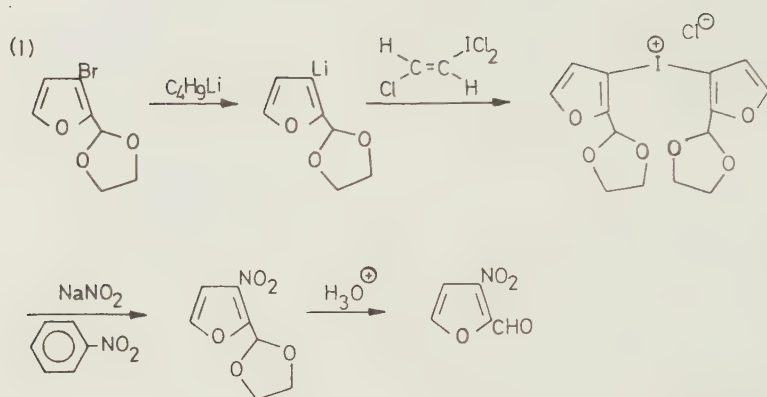
Metalation of selenophene gave 2-selenienyllithium¹¹⁰ and the following reaction with trans-chlorovinylidioso dichloride⁴² gave a 71 % yield of di-(2-selenienyl)iodonium chloride, which upon reaction with sodium nitrite in DMF, yielded 37 % of pure 2-nitroselenophene. 3-Selenienyllithium,^{11,111} prepared from 3-bromoselenophene¹¹¹ and butyllithium, gave in the same way di-(3-selenienyl)iodonium chloride in 57 % yield. From the iodonium salt 3-nitroselenophene was obtained (18 %). The lower yields of both di-(3-selenienyl)iodonium chloride and 3-nitroselenophene than of the corresponding 2-isomers, can at least in part be due to ring-opening reactions.¹¹

3-Thiocyanoselenophene was isolated in 48 % yield from the reaction of di-(3-selenienyl)iodonium chloride and sodium thiocyanate.

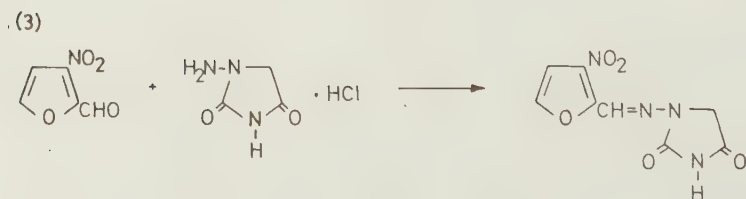
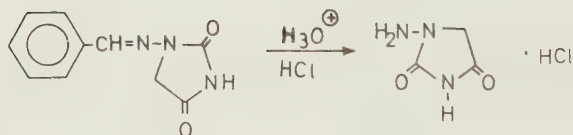
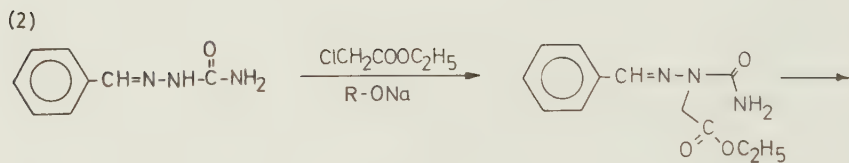
Since 3-nitrofuran could be obtained in relatively good yield, it was attractive to see if the same method would be useful also for more complex 3-nitrofuran derivatives.

Nitrofurantoin, 1-(5'-nitro-2'-furfurylideneamino)hydantoin, is a well known antibacterial drug in the treatment of infections of the urinary tract. It is prepared by the condensation of 1-aminohydantoin with 5-nitro-2-furfural or the diacetate of the latter.¹¹² The synthesis of the isomeric 1-(3'-nitro-2'-furfurylideneamino)hydantoin and the following investigation of its eventual antibacterial activity was therefore of great interest, as the nitro group in the 3- (ortho) position has similar electronic effects as the nitro group in the 5- (para) position, although steric effects are quite different.

3-Nitro-2-furfural was prepared (cf. (XXIX)) starting from



(XXIX)



2-(3-bromo-2-furyl)-1,3-dioxolane,²⁷ via 2-(3-lithio-2-furyl)-1,3-dioxolane,²⁷ di-[2-(2-(1,3-dioxolanyl))-3-furyl]iodonium chloride, and 2-(3-nitro-2-furyl)-1,3-dioxolane. 1-Benzylideneaminohydantoin can be obtained from benzaldehyde semicarbazone and ethyl monochloroacetate in the presence of sodium ethoxide in ethanol¹¹² or *t*-butoxide in *t*-butanol.¹¹³ Hydrolysis of 1-benzylideneaminohydantoin with hydrochloric acid in water then gives 1-aminohydantoin hydrochloride,¹¹² which upon condensation with 3-nitro-2-furfural leads to 1-(3'-nitro-2'-furfurylidene-amino)hydantoin. This nitrofurantoin showed however no activity when tested on bacterial cultures.¹¹³ Earlier investigations on other β -nitrofuran derivatives, such as methyl 3-nitro-2-furancarboxylate and ethyl 2-acetyl-amino-3-nitro-5-furancarboxylate, also showed that these were much less active than the α -nitroisomers.¹¹⁴ However, very few β -nitrofurans have been tested, which has been due to the inavailability of this class of compounds.

As a conclusion it is evident that iodonium salts open the route to several furan and selenophene derivatives, which are difficult to prepare by other methods and especially if isomer-free products are desired.

In Tables 19 and 20 the yields and analytical data of the prepared difuryl- and diselenenyl-iodonium chlorides, are given.

V.5 Reactions of symmetrical iodonium salts in the presence of copper salts or 1,1-diphenylethylene

Dithienyliodonium salts gave, as indicated previously, no substituted thiophenes with certain nucleophiles. Instead reduction products or tar formation was observed. The undesired side-reaction, which leads to the formation of the parent arene, as well as benzene from diphenyliodonium salts,^{80,115} is the dominating reaction with heterocyclic iodonium salts derived from furan, thiophene, or selenophene and some nucleophiles. The reaction of di-(3-thienyl)iodonium chloride with sodium methoxide in methanol gave only a total yield of 5 % of 3-methoxythiophene, additionally, 95 % of 3-iodothiophene and 74 % of thiophene was obtained. With sodium cyanide in water only 2 % of 3-cyanothiophene was formed together with 48 % of 3-iodothiophene and 2 % of thiophene. The total material

Table 19. Yields and melting points of difuryl- and diselenienyllithium chlorides obtained in the reaction of furyl- and selenienyllithium derivatives with trans-chlorovinylidioso dichloride.

Lithium derivative	Iodonium chloride	Yield (%)	Recryst. from	M.p. (°C) (dec.)
2-Furyllithium ²	Di-(2-furyl)-	35	MeOH	dec. slowly > 175
3-Furyllithium ³²	Di-(3-furyl)-	54	MeOH	249-250
2-(3-Lithio-2-furyl)- 1,3-dioxolane ²⁷	Di-[2-(2-(1,3-dioxo- lanyl))-3-furyl]-	43	MeOH	177-179
2-Selenienyllithium ¹¹⁰	Di-(2-selenienyl)-	71	Water	121-122
3-Selenienyllithium ^{11,111}	Di-(3-selenienyl)-	57	Water	170-171

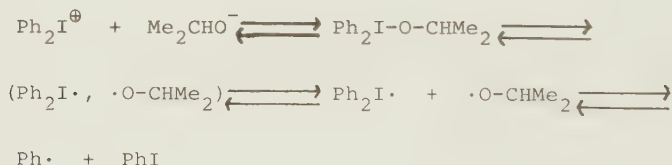
Table 20. Analytical data of difuryl- and diselenienyliodonium chlorides obtained in the reaction of furyl- and selenienyllithium derivatives with trans-chlorovinylidioso dichloride.

Iodonium chloride	Elemental analyses			Molecular formula (Molecular weight)
	Found = F			
	Calculated = C			
	C	H	I	
Di-(2-furyl)-	F. 32.4	2.14	43.0	$C_8H_6ClIO_2$ (296.6)
	C. 32.4	2.04	42.8	
Di-(3-furyl)-	F. 32.3	2.05	42.4	$C_8H_6ClIO_2$ (296.5)
	C. 32.4	2.04	42.8	
Di-[2-(2-(1,3-dioxo- lanyl))-3-furyl]-	F. 38.1	3.28	28.5	$C_{14}H_{14}ClIO_6$ (440.6)
	C. 38.2	3.20	28.8	
Di-(2-selenienyl)-	F. 22.7	1.41	30.0	$C_8H_6ClISe_2$ (422.4)
	C. 22.7	1.43	30.0	
Di-(3-selenienyl)-	F. 22.7	1.41	30.2	$C_8H_6ClISe_2$ (422.4)
	C. 22.7	1.43	30.0	

balance was not determined due to difficulties in analyzing the accompanying tarlike products. In the same manner, the reaction of di-(3-thienyl)iodonium chloride with piperidine gave only 1 % of 3-piperidinethiophene, besides 44 % of thiophene and 78 % of 3-iodothiophene. Di-(2-thienyl)iodonium chloride behaved as the 3-analogue. Thus, it is obvious that heterocyclic iodonium salts behave different from diphenyliodonium salts, because it has earlier been claimed that e.g. aqueous cyanide gives about equal amounts of benzonitrile and hydrolysis products.¹¹⁶

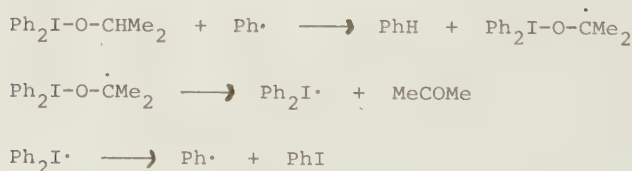
McEwen et al.¹¹⁷ found that in the reaction of phenyl-*p*-tolyliodonium tetrafluoroborate with sodium ethoxide in ethanol, a radical reaction accompanied the arylation of the ethoxide ion. Together with phenetole, *p*-methylphenetole, iodobenzene, and *p*-iodotoluene the formation of benzene and toluene was observed. Benzene and toluene were the dominant products. However, their formation could be suppressed if inhibitors of radical chain reactions, such as 1,1-diphenylethylene or diphenylpicrylhydrazyl, were added. Inhibitors such as oxygen had no effect. McEwen et al. also suggested a mechanism for the reaction between diphenyliodonium ion and sodium isopropylloxide (XXX).¹¹⁷

1. Initiation

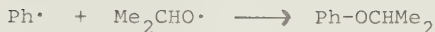


2. Propagation

(XXX)



3. Termination



Earlier it has been found that this reaction path can be initiated by peroxides¹¹⁸ and that photochemical decompositions of diphenyliodonium tetrafluoroborate in alcohol lead to benzene and iodobenzene.^{119,120} It could be confirmed that the addition of 1,1-diphenylethylene to the reaction between di-(3-thienyl)iodonium chloride and sodium methoxide in methanol suppressed the formation of thiophene and led to an increase of 3-methoxythiophene produced. To suppress the unwanted reaction leading to thiophene, large amounts of 1,1-diphenylethylene, at least equimolar to the total amount of methoxide ion and iodonium salt, have to be used (cf. Table 21). Gas chromatographic analysis revealed the appearance of peaks with much longer retention time than the simple thiophenes (columns: D, E). Two of these peaks were identified by combined vpc-mass spectrometry as 1,1-diphenyl-2-(3-thienyl)ethane and 1,1-diphenyl-2-(3-thienyl)ethene, probably arising from the reaction of 3-thienyl radicals with 1,1-diphenylethylene. It was also confirmed that diphenylpicrylhydrazyl favored the formation of 3-methoxythiophene.

The addition of 1,1-diphenylethylene in the reaction between di-(3-thienyl)iodonium chloride and sodium cyanide had no effect, and only traces of 3-cyanothiophene were formed. It was likewise found that 1,1-diphenylethylene had only slightly raised the yield of 3-nitrofuran from di-(3-furyl)iodonium chloride and nitrite ion in DMF. Thus it is obvious that 1,1-diphenylethylene can not effectively suppress the radicaloid side-reaction with all nucleophiles to make the reaction a useful one for the arylation of nucleophiles. Lubinkowski and McEwen found that diarylbromonium salts were superior arylating agents.¹²¹ The use of diarylbromonium salts is, however, limited since no convenient method for their preparation presently exists.

A possibility to increase the yield of arylated nucleophiles was to speed up the rate of the nucleophilic reaction

Table 21. The influence of 1,1-diphenylmethylene on the product distribution in the reaction between di-(3-thienyl)iodonium chloride and sodium methoxide in methanol at 70°C.

Relative molar concentration		Total yield (%)				Reaction time (h)	
Methoxide	Di-(3-thienyl)- iodonium chloride	1,1-Diphenyl- ethylene	Thiophene	3-Chloro- thiophene	3-Methoxy- thiophene	3-Iodo- thiophene	
4.85	1.00	0.97	19	-	36	82	1.0
4.94	1.00	4.38	10	-	49	86	1.0
4.77	1.00	5.68	9	-	49	88	1.0

path* over that of the competing undesired radicaloid reaction.

Nucleophilic aromatic substitution reactions are, in many instances readily promoted by copper.¹²² Beringer et al. showed that copper catalysis prevailed in the reaction between diphenyliodonium ions and halide ions.^{118,123} It was also found that copper ions strongly catalyzed the reaction of cyanide ion, but not that of nitrite ion.¹¹⁶

When the reaction of di-(3-thienyl)iodonium chloride with aqueous cyanide was studied,¹²⁴ it was found to be strongly influenced by the presence of copper sulphate (Table 22). Cyanide ion was used in fivefold excess over the iodonium salt. In the absence of copper(II) ions, only 1-2 % of 3-cyanothiophene was obtained. The addition of copper sulphate favored, however, the yield of 3-cyanothiophene. Equimolar amounts of iodonium salt and copper sulphate gave, after 3 hours at 100°, the highest yield of 3-cyanothiophene (72 %); only traces of thiophene were formed. Increasing the added amount of copper ions lowered the yields drastically of both 3-cyanothiophene and 3-iodothiophene and the formation of 3-chlorothiophene was observed.

In the reaction between di-(3-thienyl)iodonium chloride and methoxide ion in methanol (Table 23), it was likewise found that the addition of approximately one equivalent of copper salt led to the best yields of 3-methoxythiophene, although the formation of thiophene was not completely suppressed. The formation of thiophene was diminished at higher relative amounts of copper salts, but this also led to a decrease in the yield of 3-methoxythiophene due to the increase of 3-chlorothiophene. In addition to the results in Table 23, it was found that di-(3-thienyl)iodonium chloride and sodium methoxide (1.00:4.55) in DMF gave a total yield of thiophene (26 %) and 3-iodothiophene (82 %), but that neither 3-chloro- nor 3-methoxythiophene could be observed. Thus, it seems as if the reactions of chloride ions are more efficiently catalyzed by copper ions than

* This does not imply that the mechanism is necessarily the normal nucleophilic aromatic substitution.

Table 22. The influence of copper(II) sulphate on the product distribution in the reaction between di-(3-thienyl)iodonium chloride and sodium cyanide in water at 100°C.

Relative molar concentration		Total yield (%)				Reaction time (h)	
Cyanide	Di-(3-thienyl)- iodonium chloride	Copper (II) sulphate	Thiophene	3-Chloro- thiophene	3-Cyano- thiophene	3-Iodo- thiophene	
5.11	1.00	-	2	-	2	48	3.0
5.01	1.00	-	3	-	1	46	17
5.33	1.00	0.32	1	-	31	79	3.0
5.12	1.00	1.02	traces	-	72	84	3.0
4.94	1.00	5.06	-	14	11	35	3.0

Table 23. The influence of copper ions on the product distribution in the reaction between di-(3-thienyl)iodonium chloride and sodium methoxide in methanol at 70°C.

Relative molar concentration				Total yield (%)			Reaction time (h)
Methoxide	Di-(3-thienyl)- iodonium chloride	Copper salt	Thiophene	3-Chloro- thiophene	3-Methoxy- thiophene	3-Iodo- thiophene	
4.91	1.00	-	74	-	5	95	1.0
4.98	1.00	1.12 ^a	24	1	64	96	1.0
4.94	1.00	1.20 ^a	14	5	61	100	1.0
4.84	1.00	4.90 ^a	5	25	45	93	1.0
4.74	1.00	5.87 ^a	5	26	43	93	1.0
4.81	1.00	1.03 ^b	27	2	52	98	1.0
4.96	1.00	4.98 ^b	3	52	26	94	1.0
4.85	1.00	6.00 ^b	traces	76	9	93	1.0

^a CuCl.

^b CuSO₄.

methoxide ions. From Table 23 it can also be noted that the formation of 3-chlorothiophene is greater when copper sulphate is used, despite the lower concentration of chloride ion present compared to when cuprous chloride is used. This indicates that copper(II) salts are at least more effective in catalysis than copper(I) salts, opposite to the results obtained by Beringer *et al.*¹²³ They found that cuprous chloride was much more effective than cupric chloride in catalyzing the decomposition of diphenyliodonium chloride in diethylene glycol, and proposed that the induction period observed with Cu(II) was a reflection of the reduction of Cu(II) to Cu(I). In the reaction of di-(3-thienyl)iodonium chloride with piperidine in water (Table 24), it was however found that copper(I) caused the formation of more 3-chlorothiophene than did copper(II) ions. It can be assumed that the different solvents are responsible for these variations. The explanation can lie in differing solvation. The disproportionation of copper(I) ions to metallic copper and copper(II) ions, which can be influenced strongly by solvent, must also be taken into account.

The results from the reaction of di-(3-thienyl)iodonium chloride with piperidine are given in Table 24. With this nucleophile the yield of 3-piperidinothiophene could only be increased to 15 % by the addition of copper salts. This yield was obtained when the ratio of di-(3-thienyl)iodonium chloride to copper sulphate was about 10:1, or if cupric chloride was used, 3:1. Increasing the amount of copper salt, caused an increase in the formation of 3-chlorothiophene. The somewhat unexpected product di-(3-thienyl)sulphide was also formed. This product was identified with combined vpc-mass spectrometry and by comparison of an authentic sample.¹²⁵ It is noticeable that this by-product is formed in appreciable amount when copper(II) salts are added, whether sulphate or chloride is used. As the formation of di-(3-thienyl)sulphide was not observed in the reaction with other nucleophiles, it can be assumed that the sulphidic sulphur originates from decomposition of 3-piperidinothiophene. If, in this decomposition, sulphide ions are formed, they can react with the iodonium salt or 3-iodothiophene to give di-(3-thienyl)sulphide.

When the copper promoted reactions were extended in

Table 24. The influence of copper ions on the product distribution in the reaction between di-(3-thienyl)iodonium chloride and piperidine in water at 100°C.

Relative molar concentration			Total yield (%)				Reaction time (h)
Piperidine	Di-(3-thienyl)- iodonium chloride	Sodium or copper salt	Thiophene	3-Chloro- thiophene	3-Piperidino- thiophene	3-Iodo- thiophene	Di-(3-thienyl)- sulphide
4.97	1.00	-	44	-	1	78	-
5.14	1.00	1.00 ^a	43	-	traces	79	traces
4.99	1.00	0.11 ^b	23	3	15	68	10
4.90	1.00	0.33 ^c	11	41	15	76	6
4.90	1.00	0.18 ^d	6	69	10	72	1

^aNa₂SO₄.

^bCuSO₄.

^cCuCl₂.

^dCuCl.

efforts to improve the yield of 3-thiocyanothiophene from the reaction of di-(3-thienyl)iodonium chloride and sodium thiocyanate in DMF or DMSO, it was found that copper sulphate favored the formation of 3-isothiocyanothiophene and 3-chlorothiophene. Large relative amounts of copper sulphate strongly suppressed the yield of 3-thiocyanothiophene. However, even high concentrations of copper ions did not completely eliminate the formation of 3-thiocyanothiophene. If di-(3-thienyl)iodonium chloride, sodium thiocyanate, and copper sulphate were in a ratio of 1.0:3.1:3.1, the reaction mixture contained 3-thiocyano- and 3-isothiocyanothiophene in a relative amount of 1:3. The total yields of these isomers were much lower than in the absence of copper ions, due to extensive formation of 3-chlorothiophene. The same reaction in methanol in the presence of cuprous chloride showed the same tendency. Even if di-(3-thienyl)iodonium tetrafluoroborate was used instead of the chloride in a copper sulphate catalyzed reaction, the total yield of both 3-thiocyano- and 3-isothiocyanothiophene was lower than in the uncatalyzed reaction.

2-Methoxyfuran has been prepared in 42 % yield from the reaction of methyl 2-bromo-5-furancarboxylate with methoxide ion in methanol, followed by hydrolysis and decarboxylation.¹²⁶ However, attempts made to reproduce this synthetic route were not always successful; side-reactions sometimes occurred, lowering the yield of methyl 2-methoxy-5-furancarboxylate.

2,5-Dihydro-2,5-dimethoxyfuran, prepared in an electrochemical process utilizing furan, ammonium bromide and methanol, is reported to give 2-methoxyfuran in 51 % yield in an elimination reaction at 220-250°.¹²⁷

Since both 1,1-diphenylethylene and copper salts had favored the formation of 3-methoxythiophene in the reaction of di-(3-thienyl)iodonium chloride and methoxide ion, it was of interest to see if di-(2-furyl)iodonium chloride and methoxide ion would give 2-methoxyfuran. As expected, in the absence of 1,1-diphenylethylene or copper salts, di-(2-furyl)iodonium chloride and methoxide ion in methanol gave only furan and 2-iodofuran. However, when 1,1-diphenylethylene was added, 2-methoxyfuran could be isolated in 20 % yield. Copper ions were also found to be effective in catalyzing the formation of

2-methoxyfuran; for example if cuprous chloride was used as catalyzing agent, 2-methoxyfuran was obtained in 10 % yield. Even if 1,1-diphenylethylene caused a better yield of the desired product, the use of cuprous chloride is recommended, because of the necessarily large amounts of 1,1-diphenylethylene, which are needed. The relatively low yields of 2-methoxyfuran in both cases can have its explanation in the instability of 2-iodofuran,³² which gives rise to undesired side-reactions.

Since di-(3-furyl)iodonium chloride and sodium phenoxide in water did not give 3-furyl-phenyl ether, an effort was made to effect the desired reaction in methanol in the presence of cuprous chloride. Even in this case the reaction was not very successful; only 2 % of 3-furyl-phenyl ether could be isolated. The products consisted mainly of 3-chloro- and 3-iodofuran. Thus it seems as if phenoxide ions are less effectively catalyzed by copper ions than methoxide ions.

The utility of iodonium salts could also be demonstrated by the isolation of 3-thienyl-1-hexyl ether in 23 % yield from the copper sulphate catalyzed reaction of di-(3-thienyl)iodonium chloride and sodium hexoxide in *n*-hexanol.

Beringer and Falk found that nitrite ion was not catalyzed by copper salts.¹¹⁶ This could be verified in attempts to increase the yield of 3-nitrofuran from di-(3-furyl)iodonium chloride both with water and DMF as solvent in the presence of copper sulphate.

3-Chlorothiophene has earlier been prepared from 3-thienyllithium and chlorine.⁷⁰ The reactions of aryllithia with hexachloroethane were successful in the preparation of 2- and 3-chlorofuran and 2- and 3-chloroselenophene via the corresponding lithium derivatives.¹²⁸ However, the monochlorothiophenes could not be obtained by the same synthetic procedure, due to the too close boiling points of the reaction products. The observation that chloride ions are strongly catalyzed by copper ions could be utilized in the preparation of 3-chlorothiophene in 53 % yield from di-(3-thienyl)iodonium chloride and sodium chloride in a copper sulphate catalyzed reaction.

As indicated earlier all attempts to arylate fluoride and diethylmalonate ion as well as ethyl sodiooxoacetate with di-(3-thienyl)iodonium salts failed, even with copper ions

present in different solvents.

From the results obtained, it is thus obvious that the utility of iodonium salts for the arylation of nucleophiles is greatly extended by the discovery of the catalytic effect of copper salts, leading to a change in the reaction pathway, even if the reaction fails with some nucleophiles. The chemistry of copper-promoted reactions, and of organocopper compounds in general, is presently the focus of intensive investigations. Any general agreement on the mechanism of, e.g., the copper-promoted halide exchange in aromatic halides has not been adopted. A more or less concerted four-center reaction without defineable intermediates has been proposed. It has also been suggested, that the mechanism is radicaloid in character and that the copper ions alter between the Cu(I) and Cu(II) states (for review, see Ref. 122). These mechanistic alternatives, and several others, can also be suggested for the reactions of diaryliodonium salts. An alternative possibility, which can not be excluded, is the interference of copper(II) ions with the competing radical chain reaction. 3-Thienyl radicals are in this latter alternative converted to nucleophilic substitution products faster than they abstract hydrogen from its surroundings. Recent research on the role of copper ions has also taken copper(III) intermediates into consideration.^{129a}

Beringer and Bodlaender observed that titanium(III) and chromium(II) ions strongly influenced the decomposition of diaryliodonium salts.^{129b} Therefore it can, for good reasons, be anticipated that other metallic ions are also effective in catalyzing the reactions of iodonium salts with nucleophiles. It can not be excluded, that even the nucleophiles which did not give substituted thiophenes, will do so, when the proper metallic ion catalyst is found.

V.6 Reaction mechanism of iodonium salts.

Even though the purpose of this investigation of iodonium salts was to develop their use in synthesis, it was of interest to perform a few experiments to shed some light on the prevailing mechanism in the reactions between iodonium ions and nucleophiles.

In one of their early papers, Beringer et al.⁴⁴ proposed that most of the reactions between iodonium salts and nucleophiles proceeded by nucleophilic rather than radical attack on the carbon bond to iodine in the diphenyliodonium salts studied. The evidence for their assumption was that the reaction was faster with strong bases than with weak and that parallels could be drawn with the similar ethylene sulphonium ions. Furthermore they had no indications of the formation of benzene or biphenyl, the expected by-products in a radical reaction. They also founded their conclusions on the fact that by the reaction with iodonium salts, it had been possible to phenylate several sulphhydryl groups,¹³⁰ which are good radical chain terminators. Strong indications for a nucleophilic displacement reaction were also found in kinetic experiments.^{118,123,131,132}

A few years later, another investigation on the hydrolysis of iodonium salts indicated, that neither a SN_2 nor a SN_1 reaction prevailed, but that more likely a radical reaction was at hand.⁹³ The intermediacy of diphenyliodine in a radical pair has been proposed.^{80,115,116} In the reactions of diphenyliodonium salts with Grignard reagents, the products were assumed to arise from the decomposition of trisubstituted iodines.³⁹

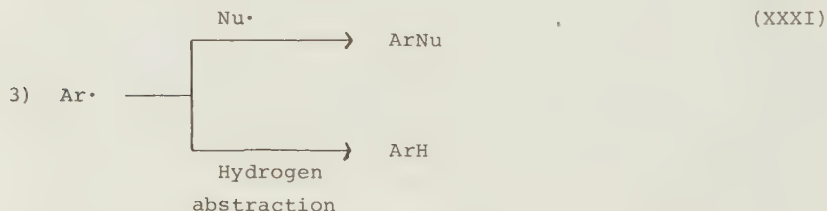
The existence of benzyne intermediates in the reactions of diphenyliodonium-2-carboxylate has also been suggested.¹³³ There was, however, no clear indication for the production of benzyne, since other reaction routes could also be derived for the products obtained.

In comparative nucleophilic substitution reactions of nitrothiophenes, it was found that 5-substituted 2-nitrothiophenes reacted faster with sodium thiopheneoxide than the corresponding 2-substituted 3-nitrothiophenes.¹³⁴ It was also observed, that the reactivity of the nitrothiophenes studied depended on the leaving group. A further observation was that the ratio of reactivity of 3-substituted 2-nitrothiophenes and 2-substituted 3-nitrothiophenes with thiopheneoxide was greater or smaller than unity depending on the leaving group. As mentioned earlier, Melander found, that thiophene should undergo nucleophilic substitution faster than benzene.⁷⁹ Thus, if a nucleophilic reaction prevailed between iodonium ions and nucleophiles, phenyl-thienyliodonium salts should give iodobenzene

and a substituted thiophene. Since mesityl-2-thienyliodonium bromides yield upon pyrolysis primarily iodothiophene and bromo-mesitylenes, it was suggested that the reaction was S_N1 like in character instead of S_N2 .⁸³

In regard of the results obtained by McEwen *et al.*^{117,119,121} and those found in this work, it is quite evident, that the reaction between iodonium salts and *e.g.* alkoxides proceeds to a great extent via radical intermediates. This radicaloid reaction was the predominating one in the case of symmetrical heterocyclic iodonium salts, and was also of importance when phenyl- and mesityl-thienyliodonium salts were reacted with methoxide ion (*cf.* V.2 and V.5).

For a radical reaction process the following scheme (XXXI) can be proposed. A nucleophile (Nu:) donates an electron to

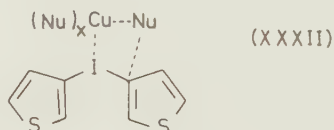


the positively charged iodine whereupon a radical pair is formed. Upon dissociation of the diaryliodonium, an aryl radical is obtained together with an aryliodine compound. If the aryl radical combines with the radical derived from the nucleophile, an arylated nucleophile is obtained; however, if the aryl radical abstracts a hydrogen atom from the surroundings a reduced aryl compound will be obtained (*cf.* also XXX). A similar reaction mechanism has also been proposed earlier.^{115,116} Beringer *et al.* found that diphenyliodonium bromide and sodium methoxide in methanol gave anisole in good yield.⁴⁴ When this reaction was repeated with diphenyliodonium chloride,³⁶ vpc analysis showed that a small amount (about 2-5 %) of benzene was

formed in addition to anisole and iodobenzene (column D). If it is assumed that the reaction between iodonium ions and nucleophiles is not nucleophilic but radicaloid in character, the more pronounced formation of thiophene from dithienyliodonium salts than benzene from diphenyliodonium salts can eventually be explained by a greater stability of phenyl than of thienyl radicals. After donation of an electron from the nucleophile to the iodonium ion and the following dissociation of the diaryliodine, the two formed radicals can be too distant from each other for combination. The electron spins of the odd electrons in the radicals can also be of unfavorable composition for combination. In such a situation, an unstable thienyl radical is quite prone to abstract a hydrogen from its surroundings. It was found that the presence of 1,1-diphenylethylene suppressed the reduction reaction. This can be due to a change in solvation of the thienyl radical.

That a change in solvation was obtained is probable, since a large amount of the inhibitor had to be used to prevent the formation of thiophene. It is possible that the 1,1-diphenylethylene stabilizes the thienyl radical in a kind of electron transfer complex. The observation of 1,1-diphenyl-2-(3-thienyl)ethane and 1,1-diphenyl-2-(3-thienyl)ethene in the reaction of di-(3-thienyl)iodonium chloride and methoxide ion in methanol in the presence of 1,1-diphenylethylene also strongly suggests the existence of thienyl radicals as intermediates. That no bi-thienyls could be detected in the reaction mixtures can be due to the instability of the thienyl radicals, since if such a radical is very short-lived it abstracts a hydrogen from its "solvation shell" faster than it combines with a second thienyl radical. The addition of copper ions also catalyzes the formation of substituted thiophenes. Here it can likewise be assumed that copper ions stabilize the thienyl radicals in an aryl-copper complex. Because both copper(I) and copper(II) ions are effective in catalyzing the formation of e.g. cyano- and methoxythiophene, the following process can be suggested. Copper(II) ions abstract an electron from the thienyl radical forming a thienyl cation and a copper(I) ion; the thienyl cation then reacts with a nucleophile to give a substituted thiophene. If copper(I) salts react in the same way, metallic copper must be

formed. Although evidence for this was not found in the reactions, it can not be excluded. A second possibility with both copper(I) and copper(II) ions is that the reaction between iodonium ions and nucleophiles in the presence of copper ions proceeds in a kind of four-center mechanism (XXXII), in which copper is bond to iodine, while the nucleophile attacks on the aryl carbon.



In the case of Cu(I) ions, a $\text{Cu}(\text{Nu})_2^-$ species can be imagined to complex with iodine, while if Cu(II) ions are used, a species with three or more ligands is thought to be the complexing agent. A further possibility is that copper(II) ions are reduced to copper(I) ions, before acting as catalysts, as indicated in earlier investigations.¹²³ The interaction of copper(III) intermediates^{129a} in the copper catalyzed reactions should of course also be taken into account.

The development of the CIDNP (Chemically Induced Dynamic Nuclear Polarization) technique has greatly extended the possibilities for studying radical reactions. Fischer and Bargon¹³⁵ observed that the thermal decomposition of dibenzoylperoxide in cyclohexanone gave rise to enhanced emission signals. Ward and Lawler¹³⁶⁻¹³⁸ obtained similar effects in the reactions of alkyl halides with alkyllithia. Theories for these effects, which can lead to both enhanced absorption and emission, have been put forward.¹³⁹⁻¹⁴²

The now accepted theory is the Kaptein-Closs theory.¹⁴³⁻¹⁴⁷ According to this theory, the reaction rate at radical combination reactions are in some cases dependent on the nuclear spin. This can lead to an enrichment of α -spins in the reaction product. If then an NMR spectrum is recorded, before relaxation of the nuclear spins, an enhanced absorption is obtained, because the population difference between α - and β -spins is greater than normal. On the other hand, if β -spins are of greater abundance in the reaction product an emission is expected. In both cases,

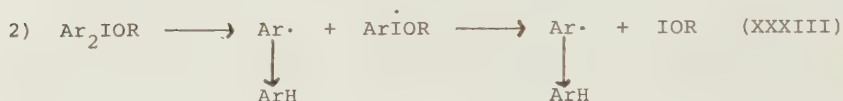
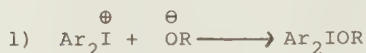
after relaxation of the nuclear spins, a normal NMR spectrum is obtained. The Kaptein-Closs theory also states that the net effect, which prevails in the case of dibenzoylperoxide, is dependent on the g-values of the reacting radicals. The g-value is that which determines the properties of the ESR signal for the radical. In some systems, e.g. in the decomposition of di-propionyl peroxide, a multiplet effect is obtained. This effect is characterized by appearance of both enhanced absorption and emission. Here the integral over a multiplet is zero. The multiplet effect is dependent upon the interaction between the electron spin and the nuclear spin by the hyperfine coupling. This interaction is responsible for the hyperfine coupling in ESR spectra. The Kaptein-Closs theory further states that:

- a) The interactions, which lead to CIDNP effects, proceed with a radical pair in a solvent cage.
- b) If two radicals will be able to react by combination or disproportionation, the radicals in the pair must be in singlet states.
- c) In such a radical pair, it is assumed that the radicals are to a degree electronically independent, that the exchange integral, between the two unpaired electrons, is of the same magnitude or smaller than the hyperfine coupling constant.
- d) A radical pair exists for about 10^{-10} seconds.

In addition to peroxides, it has also been found that e.g. 2-alkylaryldiazo sulphides upon thermal decomposition give rise to CIDNP effects.¹⁴⁸

Since it was assumed that CIDNP could give information about the reaction mechanism of dithienyliodonium salts and nucleophiles, we tried to record such spectra. While this investigation was in progress, a paper¹⁴⁹ appeared in which CIDNP effects in the reaction of diphenyliodonium salts and alkoxides had been studied. In this latter investigation it was found that if a diphenyliodonium salt dissolved in DMSO was added to a solution of sodium butoxide in butanol, emission signals were obtained. If instead, sodium methoxide in methanol was used, an enhanced absorption was the result. It was found that the products consisted of benzene and iodobenzene. In addition to this, it was observed that the relative amounts of benzene and iodobenzene formed depended on the relative concentrations of alcohol

to DMSO. The more DMSO was added the more benzene was formed. For this effect a radical mechanism, different from that above, was proposed (XXXIII). The first step leads to diarylmonooxide iodine, which in a following step dissociates to an aryl radical and an aryl alkoxide iodine. The aryl radical abstracts a hydrogen to give a reduced aryl compound. The other radical dissociates further into one aryl radical, which through hydrogen abstraction gives an unsubstituted product, and an alkoxyiodine, the fate of which was not further investigated.



When the same reactions were performed with di-(3-thienyl)iodonium chloride or tetrafluoroborate the same CIDNP effects were observed. On extension to sodium ethoxide in ethanol and sodium propoxide in propanol, it was found that ethoxide ion gave enhanced absorption and the propoxide ion emission. With all alkoxides it was observed that the effects could only be observed for a very short time. In the case of propoxide ion and di-(3-thienyl)iodonium ion, the maximal emission was obtained after approximately 5-10 seconds. For butoxide ion the emission maximum came after about 10 seconds.

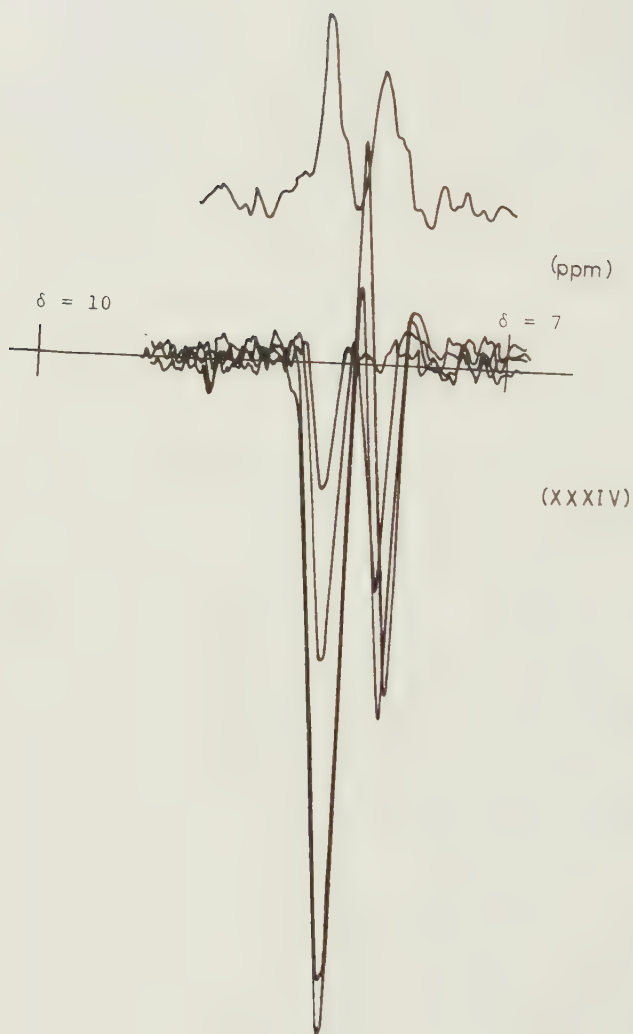
Methoxide ion gave the maximal enhanced absorption after approximately 20 second and ethoxide after 10-15 seconds.

If di-(3-thienyl)iodonium chloride was dissolved in methanol and added to methanolic sodium methoxide solution, an enhanced absorption could also be registrated. When cuprous chloride was present in the solution of butoxide ion in butanol, and di-(3-thienyl)iodonium chloride dissolved in DMSO was added, no emission signals could be detected. This is a further strong indication for the interaction of copper ions in the assumed radical reaction. Unfortunately, it was not possible to calculate the enhancement factors in the cases of methoxide and ethoxide ion, since the absorptions of the hydroxy hydrogens of respectively alcohols coalesced with those of thiophene. That

enhanced absorptions were at hand with these latter alkoxides was, however, quite evident from the fact that the actual absorption bands were strongly enhanced during a short period (< 30 seconds) after the addition of the iodonium salt.

For butoxide ion a more favorable situation prevailed and here an enhancement of about -5 was obtained. The enhancement factor for propoxide ion was of about the same magnitude. It was also observed that the absorption bands of hydroxyl groups were shifted strongly upfield, when the iodonium salts in DMSO were added. The spectra of the aryl region from the reaction of di-(3-thienyl)iodonium chloride and butoxide ion is shown below (XXXIV). An effort to get CIDNP effects in the reaction of di-(3-thienyl)iodonium chloride and sodium nitrite in DMF failed in that neither enhanced absorption nor emission could be detected.

From the results of metal ion catalysis, especially those with copper ions, and the CIDNP effects obtained, it is evident that at least some reactions of iodonium salts proceed via radicals. Even if CIDNP effects were not obtained, e.g. in the reaction of di-(3-thienyl)iodonium chloride and nitrite ion, it can not be excluded that reactions which lead to substituted thiophenes proceed via a radical mechanism. The explanation that no effects were obtained can be that the proper conditions for CIDNP effects did not prevail in the efforts with nitrite ion. It is also evident that further investigations on the reactions of iodonium salts are necessary to get a more clear picture of the reactions with nucleophiles.



NMR spectra of the aryl region from the reaction of di-(3-thienyl)-
iodonium chloride in DMSO with sodium butoxide in butanol at 40°.

VI. EXPERIMENTAL PART

VI.1 Analytical methods and remarks

Gas chromatographic analyses were performed with a Perkin-Elmer 900 apparatus equipped with a flame ionization detector and connected to a Varian 480 digital integrator. In some cases, however, a disc integrator was used for the evaluation of the gas chromatograms. The columns were made of stainless steel with 1/8" o.d. Nitrogen was used as carrier gas. The columns in Table 25, which are referred to in the text, were used for the analyses.

Table 25. Gas chromatographic columns used in connection with the experiments.

Column	Stationary phase	%	Carrier	Mesh	Length (m)
A	Neopentyl glycol succinate (NPGS)	5	Chrom. W	80/100	2.0
B	OV 17	3	Gas Chrom Q	100/120	2.5
C	Butane-1,4-diol-succinate (BDS)	10	Chrom. W	80/100	2.0
D	Neopentyl glycol sebacate (NPGS)	10	Chrom. W	80/100	2.5
E	OV 1	3	Gas Chrom Q	100/120	2.5
F	Silicon grease (DC 710)	5	Chrom. W	80/100	2.0
G	Apiezon L	5	Chrom. W	80/100	2.0
H	OV 17	3	Gas Chrom Q	100/120	3.0

Products of less than 1 % abundance in the reaction mixtures are not reported, if they are not of special interest. For all products obtained in the reactions discussed in chapters III-V, calibration was, if not otherwise stated, made for the sensitivity factor of each compound to the flame.

NMR spectra were recorded on a Varian A-60 instrument. Tetramethylsilane (TMS) was used as internal standard. A Perkin-Elmer 257 IR spectrometer was used for IR spectra. Mass spectra were recorded on a LKB 9000 mass spectrometer at 70 eV. The mass spectra were mainly used for identification of the molecular ion; no detailed study of the fragmentation pattern was made. It can be mentioned that the expected molecular ions were, with the exception of iodonium salts, obtained for all compounds isolated. The fragments of greatest abundance in the mass spectra of iodonium salts were those arising from cleavage at both sides of the iodine atom. The following fragmentation of the so obtained arylido cations did not indicate the formation of any abnormal fragments.

Melting points were taken in capillary tubes. In connection with this it was, as in other investigations,⁴¹ found that the iodonium salts decomposed near their melting points and that these depended strongly on the duration of heating. Therefore, after an approximate melting point had been taken, a new sample was introduced at about 10° below this point, and then the temperature was slowly raised. Melting points are uncorrected.

Most of the elemental analyses were performed by the Department of Analytical Chemistry at the University of Lund, Sweden, and a few by Miss Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, West Germany.

All experiments with lithium derivatives were performed under dry nitrogen atmosphere. The nitrogen gas was freed from oxygen and dried by first bubbling through a 15 % aqueous solution of pyrogallol and then through concentrated sulphuric acid. The ether used in connection with lithium derivatives was dried over sodium. Alkyl lithium solutions were first titrated on total alkali and then, after destruction of alkyl lithium, on the remaining alkali to determine the actual concentration of alkyl lithium.

The purities of the compounds were controlled by gas

chromatography and NMR. Acids were esterified with diazomethane before being injected into the gas chromatograph. Letters after "Column" in the experiments refer to the gas chromatographic columns used (cf. Table 25). In this experimental part of the thesis the preparative experiments are described. The results of the detailed product distributions are given in chapters III-V.

VI.2 Halogenated thiophenes

2-Bromo-5-chlorothiophene.

A. With NCS. To 8.2 g (0.050 mol) of 2-bromothiophene¹⁹ in 200 ml of acetic acid was added a small amount of the 6.7 g (0.050 mol) of NCS, which was totally added. The temperature was raised to reflux, whereupon the rest of the NCS was added portionswise. After refluxing for 1 hour, the reaction mixture was poured into water and extracted with ether. The combined ether phases were washed with water, diluted sodium hydroxide solution and more water. After drying over magnesium sulphate the ether was evaporated. Distillation gave 5.4 g (55 %) of 2-bromo-5-chlorothiophene at 63-67°/11 mm. Column: A. Lit. value:⁵⁰ 69.5-70.0°/18 mm.

B. With NBS. To 11.8 g (0.100 mol) of 2-chlorothiophene¹⁸ in 160 ml of acetic acid was added portionswise 18.5 g (0.104 mol) of NBS. When the reaction did not start spontaneously, it was heated to 35-40°. After stirring for 2 hours, during which time the temperature did not exceed 40°, the reaction mixture was poured into water and worked-up as above. Distillation gave 9.2 g (47 %) of 2-bromo-5-chlorothiophene at 59-60°/9 mm. Lit. value:⁵⁰ 69.5-70.0°/18 mm. Column: A. NMR (CCl₄): $\delta_{\text{ring hydrogens}}$ = 6.67 ppm and 6.74 ppm, $J_{3,4}$ = 4.0 Hz.

2-Chloro-5-iodothiophene.

A. With NCS. To 8.0 g (0.038 mol) of 2-iodothiophene²³ and 200 ml of acetic acid was added portionswise, at reflux, 5.1 g (0.038 mol) of NCS over a 15 min period. After refluxing for 4 hours the reaction mixture was poured into water and worked up as above. Distillation gave 5.1 g (55 %) of 2-chloro-5-iodothiophene at 88-90°/10 mm. Lit. value:¹⁶ 95-96°/14 mm. Column: A.

B. With iodine-HIO₃. To 11.8 g (0.100 mol) of 2-chlorothiophene,¹⁸ 43 ml of acetic acid, 16 ml of water, 21 ml of carbon tetrachloride, 3.7 g (0.021 mol) of HIO₃, and 0.7 ml of concentrated sulphuric acid was added portionswise, at reflux, 10.2 g (0.040 mol) of iodine. After reflux for 3 hours more water and carbon tetrachloride were added. The organic phase was separated, washed with water, sodium thiosulphate solution, water, and dried over magnesium sulphate. Distillation gave 12.9 g (53 %) of 2-chloro-5-iodothiophene at 86-87°/11 mm. Lit. value:¹⁶ 95-96°/14 mm. Column: A. NMR (CCl₄): $\delta_{\text{ring hydrogens}} = 6.51$ ppm and 6.95 ppm, $J_{3,4} = 3.8$ Hz.

3-Bromo-2-chlorothiophene. A solution of 82 g (0.50 mol) of 3-bromothiophene⁹ in 400 ml of acetic acid was warmed to almost reflux, whereupon 74 g (0.55 mol) of NCS was added in portions. After reflux for 5 hours the reaction mixture was poured into water and extracted with ether. The combined ether phases were washed with water, diluted sodium hydroxide solution, water, and dried over magnesium sulphate. Distillation gave 61 g (62 %) of 3-bromo-2-chlorothiophene at 69-73°/11 mm. Lit. value:⁵² 68-72°/9 mm. Column: A.

2-Chloro-3-iodothiophene. A solution of 63 g (0.30 mol) of 3-iodothiophene⁵¹ and 300 ml of acetic acid was warmed to almost reflux, whereupon 44 g (0.33 mol) of NCS was added in portions. After reflux for 3.5 hours the reaction mixture was poured into water and worked up as above. Distillation gave 39 g (53 %) of 2-chloro-3-iodothiophene at 96-98°/11 mm. Column: A. NMR (CCl₄): $\delta_{\text{ring hydrogens}} = 6.91$ ppm and 6.99 ppm, $J_{4,5} = 5.8$ Hz. Calcd. for C₄H₂ClIS (244.5): C 19.6; H 0.82; I 51.9. Found: C 19.8; H 0.92; I 51.9.

3-Bromo-2,5-dichlorothiophene. 8.2 g (0.050 mol) of 3-bromothiophene⁹ in 200 ml of acetic acid was warmed to reflux, whereupon 13.4 g (0.100 mol) of NCS was added in portions during 15 min. After reflux for 2.5 hours the reaction mixture was poured into water and worked up as above. Distillation gave 6.4 g (55 %) of 3-bromo-2,5-dichlorothiophene at 89-92°/11 mm. Column: A. Calcd. for C₄HBrCl₂S (232.0): C 20.7; H 0.43; S 13.8. Found: C 20.7; H 0.39; S 13.8.

2,5-Dichloro-3-iodothiophene. 21.0 g (0.100 mol) of 3-iodothiophene⁵¹ in 200 ml of acetic acid was warmed to reflux, whereupon 26.8 g (0.200 mol) of NCS was added in portions. The reaction was followed gas chromatographically by analysis of aliquots taken each half an hour. After reflux for 5.0 hours the product composition did not deviate from that after 4.5 hours. The reaction mixture was then poured into water and worked up as above. Distillation gave 10.8 g (39 %) of 2,5-dichloro-3-iodothiophene at 112-114°/11 mm. Column: A. Calcd. for C_4HCl_2IS (278.9): C 17.2; H 0.36; I 45.5. Found: C 17.6; H 0.48; I 45.3.

3-Bromothiophene and sulphuryl chloride. To 24 g (0.15 mol) of 3-bromothiophene⁹ was added dropwise 25 ml (0.31 mol) of sulphuryl chloride. After the addition, the mixture was refluxed for 2 hours. Vpc analysis showed that several products had been formed. Reflux for a further 2 hours did not change the result. No peak in the gas chromatogram was dominating. This method is thus not useful for the preparation of 3-bromo-2,5-dichlorothiophene. The products were not identified. Column: D.

2,3-Diiodothiophene and sulphuryl chloride. To 6.7 g (20 mmol) of 2,3-diiodothiophene,²⁴ 1.6 ml (20 mmol) of sulphuryl chloride was added dropwise. After reflux for 1.5 hours, vpc analysis showed that most of the starting material was unreacted. An additional 1.5 ml (19 mmol) of sulphuryl chloride was added, whereupon reflux was continued for 6.5 hours. Besides starting material, which was the largest peak, vpc analysis indicated the formation of 2-chloro-3-iodothiophene, 2,5-dichloro-3-iodothiophene and eventually 2,3,5-triiodothiophene. Thus this method was not useful for the preparation of 5-chloro-2,3-diiodothiophene. Column: A.

5-Chloro-2,3-dibromothiophene. 363 g (1.50 mol) of 2,3-dibromothiophene⁵³ in 1500 ml of acetic acid was warmed to reflux, whereupon 210 g (1.57 mol) of NCS was added. The reaction mixture first turned to light green but darkened after a while. Vpc analysis was used to follow the reaction. After reflux for 24 hours the reaction mixture was poured into water and extracted with ether. Tarlike products were filtered off. The water phase was extracted with more ether. The combined ether

phases were washed with water, diluted sodium hydroxide solution, water and dried over magnesium sulphate. Distillation, utilizing a 35 cm long column filled with glass helices, gave 150 g (36 %) of 5-chloro-2,3-dibromothiophene at 106-109°/11 mm. Column: B. Calcd. for C_4HBr_2ClS (276.4): C 17.4; H 0.36; S 11.6. Found: C 17.5; H 0.33; S 11.6.

2-Chloro-3,5-dibromothiophene. 24.2 g (0.100 mol) of 2,4-dibromothiophene,⁵⁴ 13.4 g (0.100 mol) of NCS and 200 ml of acetic acid were stirred at reflux for 6 hours. After work-up and distillation as above 12 g (43 %) of 2-chloro-3,5-dibromothiophene was obtained at 104-108°/10 mm. Column: B. Calcd. for C_4HBr_2ClS (276.4): C 17.4; H 0.36; S 11.6. Found: C 17.5; H 0.42; S 11.4.

2,5-Dibromothiophene and NCS. 12 g (0.050 mol) of 2,5-dibromothiophene,¹⁹ 6.7 g (0.050 mol) of NCS, and 100 ml of acetic acid were stirred at reflux for 5 hours. After work-up as above, vpc analysis on the ether phase showed that several products had been formed. No 3-chloro-2,5-dibromothiophene could be identified with certainty, because of difficulties in the separation of the products in the reaction mixture. Column: C.

2-Bromo-5-iodothiophene. To 7.1 g (0.034 mol) of 2-iodothiophene²³ in 200 ml of acetic acid was added 6.0 g (0.034 mol) of NBS in portions over 15 min. After stirring for an additional 1.5 hours the reaction mixture was poured into water and worked up as above. Distillation gave 3.7 g (38 %) of 2-bromo-3-iodothiophene at 107-110°/11 mm. Lit. value:¹⁵⁰ 116°/13 mm. Column: C. NMR (CCl_4): $\delta_{\text{ring hydrogens}} = 6.67 \text{ ppm and } 6.95 \text{ ppm, } J_{3,4} = 3.8 \text{ Hz.}$

2-Bromo-3-iodothiophene. To 21.0 g (0.100 mol) of 3-iodothiophene⁵¹ in 150 ml of acetic acid was added 18.5 g (0.104 mol) of NBS. After stirring for 30 min the reaction mixture was poured into water and worked up as above. Distillation gave 24 g (83 %) of 2-bromo-3-iodothiophene at 104-108°/8 mm. Column: A. NMR: $\delta_{\text{ring hydrogens}} = 6.91 \text{ ppm and } 7.17 \text{ ppm, } J_{4,5} = 5.6 \text{ Hz.}$ Calcd. for C_4H_2BrIS (288.9): C 16.6; H 0.70; S 11.1. Found: C 16.7; H 0.81; S 10.9.

2,5-Dibromo-3-iodothiophene.

A. With iodine- HIO_3 . To 115 g (0.48 mol) of 2,5-dibromothiophene,¹⁹ 200 ml of acetic acid, 75 ml of water, 100 ml of concentrated sulphuric acid, and 18 g (0.10 mol) of HIO_3 was added, at reflux, 48 g (0.19 mol) of iodine in portions. After reflux for 24 hours more water and carbon tetrachloride were added. The organic phase was separated and washed with water, sodium thiosulphate solution, water and dried over magnesium sulphate. The carbon tetrachloride was evaporated and the residue recrystallized from ethanol, whereupon 26 g of product precipitated. After filtering, the ethanol was concentrated to about 1/3. In the refrigerator more crystals fell out. The first crystals, which contained a small amount of 2,3,5-triiodothiophene, showed a broad melting point interval. Both of the crystalline crops were then mixed together for distillation, and 18 g (11 %) of 2,5-dibromo-3-iodothiophene was obtained at 142-144°/9 mm. Columns: A, C. Calcd. for $\text{C}_4\text{HBr}_2\text{IS}$ (367.8): C 13.1; H 0.27; I 34.5. Found: C 13.2; H 0.24; I 33.5.

B. With NBS. 10.5 g (0.0500 mol) of 3-iodothiophene, 17.8 g (0.100 mol) of NBS, and 250 ml of acetic acid, were stirred at room temperature for 19 hours. The reaction mixture was poured into water and extracted with ether. The combined ether phases were washed with water, diluted sodium hydroxide solution, water and dried over magnesium sulphate. Distillation gave 8.0 g (44 %) of 2,5-dibromo-3-iodothiophene at 145-150°/11 mm. Higher temperatures and shorter reaction reaction times did not improve the yield.

5-Bromo-2,3-diiodothiophene.

A. To 25 g (0.074 mol) of 2,3-diiodothiophene²⁴ in 125 ml of acetic acid was added 14 g (0.078 mol) of NBS. As the reaction did not start spontaneously, the reaction mixture was warmed to 50°, whereupon the external heating was interrupted. After stirring for 48 hours at room temperature, vpc analysis showed that not all of the starting material was consumed. The temperature was raised to 50° and stirring was continued for further 48 hours. After work-up as above, distillation was performed. It was, however, not possible to obtain pure 5-bromo-2,3-di-

iodothiophene by distillation. The product was stored for further purification in connection with experiment B below. Column: C. B. To 100 g (0.30 mol) of 2,3-diiodothiophene²⁴ in 500 ml of acetic acid was added, in portions while heating, 54 g (0.30 mol) of NBS. After reflux for 4.5 hours the reaction mixture was poured into water and worked up as above. After evaporation of the ether the product from experiment A above was added. From distillation, two fractions were collected at 102-116°/0.2 mm and 116-119°/0.2 mm. Vpc analysis showed that the second fraction was the purest and contained about 95 % of 5-bromo-2,3-diiodothiophene and 5 % of 2,5-dibromo-3-iodothiophene. A further distillation did not improve the purity. To obtain a pure product the fractions above were chromatographed on a column filled with neutral aluminium oxide. Petroleum ether 30-50° was used as eluent. The fractions were controlled by vpc. After a few fractions pure 5-bromo-2,3-diiodothiophene was eluted. The first impure fractions were re-chromatographed, giving another crop of pure 5-bromo-2,3-diiodothiophene. After removal of the petroleum ether, 8.2 g of pure 5-bromo-2,3-diiodothiophene (m.p. 45-46°) was obtained, corresponding to an average yield of 5.3 % in experiments A and B. Column: C. Calcd. for C₄HBrI₂S (414.8): C 11.6; H 0.24; I 61.2. Found: C 11.9; H 0.28; I 60.0.

3-Iodothiophene and bromine. To 21 g (0.10 mol) of 3-iodothiophene⁵¹ in 15 ml of carbon tetrachloride, 11 ml (0.21 mol) of bromine in 15 ml of carbon tetrachloride was added over 2 hours. After stirring at room temperature for 24 hours, the reaction mixture was refluxed for 45 min. More carbon tetrachloride and 30 ml of 5 N sodium hydroxide were added. After reflux for 2 hours the reaction mixture was filtered. The separated solid tarlike product did not dissolve in boiling dioxane, but upon treatment with acetone, red-brown crystals were obtained after filtering. These crystals were only to a small degree soluble in carbon tetrachloride, which, however, was a better solvent than acetone, dimethyl sulphoxide, or chloroform. NMR spectrum did not show any proton absorptions. Combined vpc-mass spectrometry indicated that the crystals consisted of one or more hexabromobithienyls.

The filtrate above contained mainly 2,3,5-tribromothiophene.

2,5-Dibromo-3-iodothiophene could not be detected in the reaction mixture. If acetic acid was used as solvent no hexabromobithienyl could be observed. In this case 2,5-dibromo-3-iodothiophene was formed together with other products. Vpc analysis indicated that if acetic acid is used as solvent, molecular bromine can be an alternative to the utilization of NBS for the synthesis of 2,5-dibromo-3-iodothiophene. Column: B.

2,3-Diiodothiophene and bromine. To 9.0 g (0.027 mol) of 2,3-diiodothiophene²⁴ in 10 ml of carbon tetrachloride was added dropwise during a 35 min period 1.6 ml (0.031 mol) of bromine dissolved in 10 ml of carbon tetrachloride. After stirring for 24 hours, vpc analysis indicated that only products with retention times shorter than 2,3-diiodothiophene had been formed, with the exception of one product with a longer retention time. This product, which possibly was 2-bromo-4,5-diiodothiophene, was however only approximately 3 % of the total product distribution. Thus, this route is not useful for the synthesis of 5-bromo-2,3-diiodothiophene. The other products were not identified. Column: B.

2-Bromo-3,5-diiodothiophene. 5.8 g (20 mmol) of 2-bromo-3-iodothiophene, 9 ml of acetic acid, 3.5 ml of water, 4.5 ml of carbon tetrachloride, 0.2 ml of concentrated sulphuric acid, and 0.80 g (4.6 mmol) of iodic acid was heated to reflux; 2.1 g (8.3 mmol) of iodine was then added in portions. After reflux for additional 4 hours more water and carbon tetrachloride were added. The organic phase was separated and washed with water, sodium thiosulphate solution, water, and dried over magnesium sulphate. The carbon tetrachloride was evaporated and the residue recrystallized from ethanol, whereupon 2-bromo-3,5-diiodothiophene precipitated, weighing after drying 4.4 g (53 %). M.p.: 63-64°. Column: B. Calcd. for C_4HBrI_2S (414.8): C 11.6; H 0.24; I 61.2. Found: C 11.6; H 0.21; I 60.9.

3-Bromo-2-iodothiophene. 41 g (0.25 mol) of 3-bromothiophene,⁹ 80 ml of acetic acid, 30 ml of water, 20 ml of carbon tetrachloride, 1.5 ml of concentrated sulphuric acid, 20.4 g (0.080 mol) of iodine, and 8.2 g (0.047 mol) of HIO_3 were stirred at 40° until the iodine was consumed (2 hours). Water, sodium hydrogen carbonate solution, and 20 ml of carbon tetrachloride

were added. The organic phase was separated, washed with sodium hydrogen carbonate solution and dried over magnesium sulphate, whereupon it was chromatographed on a column filled with basic aluminium oxide. Low boiling petroleum ether was used as eluent. After evaporation of the petroleum ether, distillation gave 38 g (66 %) of 3-bromo-2-iodothiophene at 108-110°/9 mm. Column: A. NMR (CCl_4): $\delta_4 = 7.30$ ppm and $\delta_5 = 7.80$ ppm, $J_{4,5} = 5.6$ Hz. Calcd. for $\text{C}_4\text{H}_2\text{BrIS}$ (288.9): C 16.6; H 0.70; S 11.1. Found: C 16.8; H 0.74; S 11.2.

VI.3 Reactions of thienyllithium derivatives

Halogen-metal interconversion on 2-bromo-3-iodothiophene. To 80 ml of 0.98 M, (0.078 mol) of ethyllithium in ether cooled to below -110°, 14.5 g (0.050 mol) of 2-bromo-3-iodothiophene in 15 ml of ether was added at such a rate that the temperature was kept below -100°. After stirring for 15 min the reaction mixture was protonated with ethanol. The solution was poured into water. The ether phase was separated, washed with water, and dried over magnesium sulphate.

In a corresponding run the reaction mixture was carbonated by careful addition of dry ice to avoid temperature rise. After stirring for 45 min at -100° the reaction mixture was poured into water. The ether phase was extracted several times with diluted sodium hydroxide solution. The combined water phases were then acidified with 5 N hydrochloric acid, whereupon a mixture of carboxylic acids precipitated.

When the corresponding reactions were performed at -70°, the temperature was kept below -60°. By protonation the reaction mixture was poured into ethanol and by carbonation onto dry ice in dry ether.

Combined vpc-mass spectrometry gave the results reported in chapter IV. Columns: A, F.

2-Bromo-3-thiophenecarboxylic acid. To 80 ml of 0.98 M (0.078 mol) ethyllithium in ether was added, at -110°, 14.5 g (0.0500 mol) of 2-bromo-3-iodothiophene in 15 ml of ether with such a rate that the temperature was kept below -100°. After stirring for 15 min dry ice was added carefully to avoid a temperature

rise. Stirring was then continued for 45 min at -100° . After hydrolysis with water, the ether phase was separated and extracted several times with dilute sodium hydroxide solution. The combined water phases were acidified with dilute hydrochloric acid, whereupon 8.6 g of crude acid precipitated. 4.9 g of the crude acid was recrystallized from water, to yield 3.5 g (46 % based on recrystallized product) of pure 2-bromo-3-thiophenecarboxylic acid melting at $176-178^{\circ}$ (corrected $178-179^{\circ}$). Lit. value:⁶⁸ $178-179^{\circ}$. Column: A. NMR (acetone): $\delta_{\text{ring hydrogens}} = 7.41 \text{ ppm}$ and 7.54 ppm , $\delta_{\text{COOH}} = 9.20 \text{ ppm}$, $J_{4,5} = 5.8 \text{ Hz}$.

Efforts to trap dehydrothiophene. To 65 ml of 0.88 M (0.057 mol) ethyllithium in ether and 4.1 g (0.060 mol) of furan, 14.5 g (0.050 mol) of 2-bromo-3-iodothiophene dissolved in 15 ml of ether was added at such a rate that the temperature stayed below -60° . After stirring for 10 min, it was protonated with 40 ml of ethanol. The reaction mixture was poured into water. The water phase was extracted with ether and dried over magnesium sulphate, whereupon the combined ether phases were analyzed by vpc. No condensation product of furan and dehydrothiophene could be detected. Distillation of the product mixture did not indicate any formation of products arising from dehydrothiophene. Column: A.

Halogen-metal interconversion on 2,5-dibromo-3-iodothiophene. 5.5 g (0.015 mol) of 2,5-dibromo-3-iodothiophene dissolved in ether was cooled to -70° , whereupon 28 ml of 0.55 M (0.015 mol) butyllithium in ether was added at such a rate that the temperature was kept below -60° . After stirring for 10 min at -70° , the reaction mixture was poured into water. After work-up in the usual manner, vpc analysis showed that several products had been produced, indicating rapid rearrangement reactions. The method was therefore not suitable for the preparation of 2-bromo-4-iodothiophene. Column: C.

2-Bromo-4-iodothiophene. 120 ml of 0.90 M (1.08 mol) butyllithium in ether was cooled to -70° , whereupon 33.6 g (0.100 mol) of 2,4-diiodothiophene²⁴ dissolved in 100 ml of ether was added in a slow stream. After stirring for further 20 min, bromine, dried with concentrated sulphuric acid, was added,

while the temperature was kept at -70° . The bromine was added in portions, and in even intervals aliquots were analyzed by vpc after hydrolysis. When the ratio between 3-iodothiophene and 2-bromo-4-iodothiophene no longer declined according to their relative concentrations in the reaction mixture, the addition of bromine was interrupted. After pouring the reaction mixture into water, the ether phase was separated and the water phase extracted with ether. The combined ether phases were washed with sodium thiosulphate solution, dilute sodium hydroxide solution, water and dried over magnesium sulphate. Distillation gave 10.5 g (36 %) of 2-bromo-4-iodothiophene of $106-108^{\circ}/10$ mm. The product was further purified with preparative gas chromatography (BDS 20 % on Chrom. W, $3/8"$ x $6'$). Column: C. NMR (CCl_4): $\delta_{\text{ring hydrogens}} = 6.95$ ppm and 7.20 ppm, $J_{3,5} = 1.5$ Hz. Calcd. for $\text{C}_4\text{H}_2\text{BrIS}$ (288.9): C 16.6; H 0.70; I 43.9. Found: C 17.0; H 0.84; I 43.6.

Halogen-metal interconversion on 2-bromo-4-iodothiophene. 5.0 ml of 1.12 M (5.6 mmol) butyllithium in ether was cooled to -70° , whereupon 1.1 g (3.8 mmol) of 2-bromo-4-iodothiophene dissolved in 5 ml of ether was added with such a rate that the temperature was kept below -60° . After stirring for further 20 min, carbon dioxide gas, dried by bubbling through concentrated sulphuric acid, was led into the reaction mixture during 45 min at -70° . If protonation instead was desired, ethanol was added after stirring for 20 min. Work-up and analyses were performed as in the halogen-metal interconversion reactions with 2-bromo-3-iodothiophene (cf. above). When the reaction was performed at about -110° , the same method was used while keeping the temperature below -100° . The results of the analyses are given in Table 3. Columns: A, C.

2-Chloro-3-thiophenecarboxylic acid.

A. From 2-chloro-3-iodothiophene. To 50 ml of 0.90 M (0.045 mol) of butyllithium in ether was added, at -70° , 10 g (0.041 mol) of 2-chloro-3-iodothiophene dissolved in ether with such a rate that the temperature was kept below -55° . After stirring for 15 min the reaction mixture was poured onto dry ice in ether. When the bubbling of the carbon dioxide had finished, the mixture was

hydrolyzed with water and acidified with hydrochloric acid. After extracting the water phase with ether, the combined ether phases were extracted several times with dilute sodium hydroxide. The combined water phases were acidified with hydrochloric acid, whereupon the acid precipitated. After recrystallization from water-ethanol (1:1) and drying, 3.4 g (51 %) of 2-chloro-3-thiophenecarboxylic acid was obtained with m.p. 162-163°. Lit. value:⁶⁸ 163°. Column: C. NMR (DMSO): $\delta_{\text{ring hydrogens}} = 7.38 \text{ ppm}$ and 7.50 ppm , $\delta_{\text{COOH}} = 9.08 \text{ ppm}$, $J_{4,5} = 5.8 \text{ Hz}$.

B. From 3-bromo-2-chlorothiophene. The same method as above utilizing 3-bromo-2-chlorothiophene gave a 58 % yield of 2-chloro-3-thiophenecarboxylic acid. Column: C.

4-Bromo-2-chlorothiophene. 450 ml of 0.87 M (0.40 mol) butyllithium in ether was cooled to -70°, whereupon 96.5 g (0.350 mol) of 5-chloro-2,3-dibromothiophene dissolved in 200 ml of ether was added in a slow stream. After stirring for 20 min the reaction mixture was poured into water and worked up in the usual manner. Distillation gave 36.3 g (53 %) of 4-bromo-2-chlorothiophene at 68.0-71.5°/10 mm. Lit. value:⁷⁰ 70-72°/12 mm. Column: A.

2-Chloro-4-thiophenecarboxylic acid. 40 ml of 0.82 M (0.033 mol) butyllithium in ether was cooled to -70°, whereupon 6.0 g (0.030 mol) of 4-bromo-2-chlorothiophene dissolved in 30 ml of ether was added in a slow stream keeping the temperature below -48°. After stirring for further 20 min, the reaction mixture was poured onto dry ice in ether. Water was added and the ether phase separated and extracted with dilute sodium hydroxide solution. The combined water phases were acidified with hydrochloric acid, whereupon the acid precipitated. Recrystallization from water-ethanol (1:1) gave 2.3 g (47 %) of 2-chloro-4-thiophenecarboxylic acid with m.p. 163-164°. Lit. value:⁶⁹ 156-157°. Column: B. NMR (acetone): $\delta_3 = 7.39 \text{ ppm}$ and $\delta_5 = 8.14 \text{ ppm}$, $\delta_{\text{COOH}} = \text{broadens}$, $J_{3,5} = 1.6 \text{ Hz}$.

2-Chloro-4-iodothiophene. 70 ml of 0.89 M (0.062 mol) butyllithium in ether was cooled to -70°, whereupon 11 g (0.056 mol) of 4-bromo-2-chlorothiophene dissolved in 60 ml of ether was added in a slow stream keeping the temperature below -60°. After

stirring for an additional 25 min, the reaction mixture was poured through a rubber tube into a solution of 14.2 g (0.056 mol) of iodine in 70 ml of ether, also cooled to -70° . Stirring was then continued for 1 hour at -70° . The cooling bath was removed, and after the temperature had reached 0° , the reaction mixture was poured into water. After separation of the ether phase, the water phase was extracted with ether. The combined ether phases were washed with water, sodium thiosulphate solution, water and dried over magnesium sulphate. Distillation gave 6.0 g (44 %) of 2-chloro-4-iodothiophene at $89.5-91.5^{\circ}/10$ mm. Column: A. NMR (CCl_4): $\delta_{\text{ring hydrogens}} = 7.14$ ppm and 7.36 ppm, $J_{3,5} = 1.5$ Hz. Calcd. for $\text{C}_4\text{H}_2\text{ClI}$ (244.5): C 19.6; H 0.82; I 51.9. Found: C 19.6; H 0.86; I 50.2.

3-Iodo-2-thiophenecarboxylic acid. To 15 ml of 1.00 M (0.015 mol) ethyllithium in ether cooled to -70° was added 4.8 g (0.014 mol) of 2,3-diiodothiophene²⁴ dissolved in ether. The temperature was kept below -60° . After stirring for an additional 10 min, the reaction mixture was carbonated and worked up as for 2-chloro-4-thiophenecarboxylic acid. Recrystallization from water-ethanol (1:1) gave 1.6 g (45 %) of 3-iodo-2-thiophenecarboxylic acid with m.p. $199-201^{\circ}$. Lit. value:¹⁵¹ $193-195^{\circ}$. Column: A. NMR (acetone): $\delta_4 = 7.33$ ppm and $\delta_5 = 7.77$ ppm, $\delta_{\text{COOH}} = 7.95$ ppm, $J_{4,5} = 5.1$ Hz.

Stability of 2-chloro-3-thienyllithium. 57 ml of 0.51 M (0.029 mol) butyllithium in ether was cooled to -70° , whereupon 5.0 g (0.025 mol) of 3-bromo-2-chlorothiophene dissolved in ether was added, keeping the temperature below -55° . After stirring for 10 min the cooling bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was carbonated and worked up in the usual manner. The resulting acid mixture was esterified with diazomethane. Combined vpc-mass spectrometry showed the formation of methyl 2-chloro-5-thiophenecarboxylate, methyl 2-chloro-3-thiophenecarboxylate and methyl 3-bromo-2-chloro-5-thiophenecarboxylate. NMR spectrum on the acid mixture also indicated the formation of 2-chloro-5-thiophenecarboxylic acid ($J = 4.1$ Hz) and 2-chloro-3-thiophenecarboxylic acid ($J = 5.8$ Hz). IR analysis of

the ether phase did not reveal the formation of any compounds containing carbon-carbon triple bonds, indicating that no ring-opening reaction had occurred.

When 2-chloro-3-iodothiophene was used in a corresponding reaction, methyl 2-chloro-5-thiophenecarboxylate and methyl 2-chloro-3-thiophenecarboxylate were formed. However, in this case, no methyl 2-chloro-3-iodo-5-thiophenecarboxylate was obtained. IR analysis gave the same result as above. The results are given in Table 4. Column: C.

Stability of 2-chloro-4-thienyllithium. To 40 ml of 0.85 M (0.034 mol) butyllithium in ether was added 6.2 g (0.031 mol) of 4-bromo-2-chlorothiophene in 70 ml of ether, keeping the temperature below -51° . After stirring for an additional 15 min at -70° , the cooling bath was removed and the reaction mixture stirred for 19 hours at room temperature. One sample was taken up and hydrolyzed with water, a second sample was carbonated, and a third part was stirred at room temperature for an additional 24 hours. By absorption at approximately 2180 cm^{-1} , IR analysis of the ether phase indicated the formation of acetylenic products from ring-opening reactions. Combined vpc-mass spectrometry also indicated the prevalence of acetylenic compounds. The carbonated product was worked up and esterified. However, no methyl thiophenecarboxylates could be observed upon analysis, which also indicates that ring-opening had occurred. Analysis of the part of the reaction mixture which was stirred for a longer period gave the same result. Columns: C, G.

2-Thienyllithium and NCS or NBS. To a 2-thienyllithium¹ solution, prepared from 6.7 g (0.080 mol) of thiophene dissolved in 25 ml of ether and 100 ml of 0.98 M (0.098 mol) butyllithium in ether, 10.7 g (0.080 mol) of NCS was added. After stirring for 1 hour the reaction mixture was poured into water and worked up in the usual manner. Vpc analysis of the ether phase showed that no 2-chlorothiophene had been formed. A corresponding run with NBS gave no 2-bromothiophene. Columns: A, G.

3-Bromo-2-chloro-5-thiophenecarboxylic acid. To 40 ml of 0.85 M (0.034 mol) butyllithium in ether was added 8.2 g (0.030 mol) of 2-chloro-3,5-dibromothiophene in 30 ml of ether in a slow stream keeping the temperature below -47° . After stirring for an addi-

tional 20 min at -70° , the reaction mixture was poured onto dry ice in ether. After work-up in the usual manner and recrystallization from water-ethanol (1:1) 4.5 g (62 %) of 3-bromo-2-chloro-5-thiophenecarboxylic acid (m.p. $206-207^{\circ}$) was obtained. Column: A. Calcd. for $C_5H_2BrClO_2S$ (241.5): C 24.9; H 0.83; S 13.3. Found: C 24.8; H 0.85; S 13.2.

4-Bromo-2-chloro-5-thiophenecarboxylic acid. To 40 ml of 0.85 M (0.034 mol) butyllithium in ether cooled to -70° , was added 8.6 g (0.031 mol) of 5-chloro-2,3-dibromothiophene in 40 ml of ether in a slow stream, keeping the temperature below -42° . After stirring for an additional 20 min at -70° , the reaction mixture was carbonated and worked up in the usual way. The crude acid was recrystallized from water-ethanol (1:1), whereupon 5.0 g (67 %) of 4-bromo-2-chloro-5-thiophenecarboxylic acid (m.p. $198-199^{\circ}$) was obtained. Column: A. Calcd. for $C_5H_2BrClO_2S$ (241.5): C 24.9; H 0.83; S 13.3. Found: C 24.9; H 0.80; S 13.4.

3-Bromo-4-chlorothiophene. To a 4-bromo-3-thienyllithium⁸⁵ solution, prepared from 97 g (0.40 mol) of 3,4-dibromothiophene⁹ in 150 ml of ether and 370 ml of 1.13 M (0.42 mol) butyllithium in hexane, 100 g (0.42 mol) of hexachloroethane dissolved in 300 ml of ether was added at -70° . After stirring at -70° for 2.5 hours the cooling bath was removed; after the temperature had risen to 0° , the reaction mixture was poured into water. The ether phase was separated and the water phase extracted with ether, whereupon the combined ether phases were washed with water and dried over magnesium sulphate. Distillation gave 49 g (62 %) of 3-bromo-4-chlorothiophene at $76-80^{\circ}/10$ mm. Column: C. NMR ($CDCl_3$): δ_{ring} hydrogens = 7.17 ppm and 7.27 ppm, $J_{2,5} = 3.6$ Hz. Calcd. for C_4H_2BrClS (197.5): C 24.3; H 1.02. Found: C 24.2; H 1.18.

VI.4 Syntheses of iodonium salts

Phenyl-thienyliodonium chlorides. General procedure.

To a thienyllithium solution, prepared from 0.10 mol of thiophene or bromothiophene in 30 ml of ether and 0.11 mol of commercial butyllithium in hexane was rapidly added, at -70° , 0.10 mol of iodosobenzene dichloride⁷⁸ and 100 ml of ether. The

mixture was stirred at -70° for 3 hours, whereupon the cooling bath was removed and stirring was continued at room temperature during the night. This stirring overnight generally increased the yields of iodonium chlorides. The reaction mixture was then poured into water, the solid phase filtered off and washed with water, acetone, ether, dried and directly used for synthesis. Yields, analytical data, and references to the preparations of the thienyllithium derivatives are given in Tables 5 and 6.

Iodosomesitylene dichloride. 123 g (0.50 mol) of iodosomesitylene²³ and 150 ml of dry hexane, in a flask protected from light, was cooled to -55° , whereupon dried chlorine gas was introduced during 2 hours through a tube, ending about 1 cm above the surface of the solution. The yellow crystalline mass was filtered off and dried for 15 min on glass filter with air suction. Iodosomesitylene dichloride was, in all runs, obtained in more than 80 % yield. If stored at about -20° the iodoso dichloride was stable for several days. If chloroform or acetic acid were used as solvents the iodosomesitylene dichloride was much more prone to undergo rearrangement. NMR (DMSO D_6): $\delta_{CH_3} = 2.27$ ppm (3H), $\delta_{CH_3} = 2.43$ ppm (6H), $\delta_{ring\text{ hydrogens}} = 6.97$ ppm (2H). Couplings were not resolved.

Mesityl-thienyliodonium chlorides. General procedure.

Using iodosomesitylene dichloride, the same method as in the preparation of phenyl-thienyliodonium chlorides was used. The salts were directly used for synthesis. Yields, analytical data and references to the preparations of the thienyllithium derivatives are given in Tables 8 and 9.

p-Anisyl-3-thienyliodonium chloride. 58 g (0.26 mol) of p-iodoanisole in 150 ml of dry hexane, in a flask protected from light, was cooled to -50° and dry chlorine gas was introduced over a 1.5 hour period through a tube ending about 1 cm above the surface of the solution. The temperature was kept at -60° to -50° . At the same time a 3-thienyllithium solution⁸ was prepared from 100 ml of 1.60 M (0.16 mol) butyllithium in hexane and 24 g (0.15 mol) of 3-bromothiophene⁹ in 50 ml of ether. When the introduction of the chlorine gas was complete, the p-iodosoanisole dichloride was filtered off and kept for a few

minutes at room temperature to remove the excess of chlorine. The iodoso dichloride was very unstable at room temperature, and therefore it was, after a thorough drying, added rapidly to the 3-thienyllithium solution, which was cooled to -70° . After a while it was evident that not all of the yellow iodoso dichloride had been consumed by the added thienyllithium solution, due to the iodoso dichloride not being completely free from chlorine gas when added. A new thienyllithium solution was prepared and parts of this were added until the iodoso dichloride was consumed. After stirring for 3 hours at -70° , the cooling bath was removed and stirring was continued overnight at room temperature. After work-up as above 5.3 g (5 %) of crude p-anisyl-3-thienyliodonium chloride was obtained. Recrystallization from water (m.p. $196-198^{\circ}$) did not give a quite pure salt as shown by elemental analysis for iodine. Calcd. for $C_{11}H_{10}ClIOS$ (352.6): I 36.0. Found: I 32.5. The crude salt was used for reaction with sodium nitrite.

Phenyl-[2-(2-(1,3-dioxolanyl))-3-furyl]iodonium chloride. To a 2-(3-lithio-2-furyl)-1,3-dioxolane solution²⁷, prepared from 5.5 g (0.025 mol) of 2-(3-bromo-2-furyl)-1,3-dioxolane²⁷ in 30 ml of ether and 19 ml of 1.43 M (0.027 mol) butyllithium in hexane, there was added at -70° , 7.0 g (0.025 mol) of iodosobenzene dichloride.⁷⁸ After stirring for 2 hours at -70° the cooling bath was removed, whereupon stirring was continued at room temperature overnight. The solid product was filtered off and washed with ether. As the product of crude phenyl-[2-(2-(1,3-dioxolanyl))-3-furyl]iodonium chloride was stable just a few minutes after filtering, it was, after drying on a glass filter for a few minutes, directly used for reaction with sodium nitrite.

Symmetrical dithienyliodonium chlorides. General procedure.

To 0.10 mol of trans-chlorovinylidoso dichloride⁴² in 200 ml of dry toluene cooled to -70° , a thienyllithium solution was transferred through a rubber tube. The thienyllithium solution was prepared from 0.20 mol of thiophene or bromothiophene in 100 ml of ether and 0.21 mol of commercial butyllithium in hexane. The mixture was stirred at -70° for 2-3 hours, whereupon the cooling bath was removed. When the temperature had risen to

0°, the mixture was poured into water and the precipitated iodonium salt filtered off, washed with water, acetone and ether, dried and directly used for synthesis. Yields, analytical data, and references to the preparations of the thienyl-lithium derivatives are given in Tables 11 and 12. The salts should, in order to minimize decomposition, be stored at about 0°, if not used within a few days.

Di-(3-thienyl)iodonium tetrafluoroborate. 10 g (0.030 mol) of di-(3-thienyl)iodonium chloride was dissolved in 200 ml of boiling water, whereupon a silver tetrafluoroborate solution, prepared by dissolving 5.5 g (0.024 mol) of silver oxide in 20 g of 35 % hydrogen tetrafluoroborate solution, was added. The formed silver chloride was filtered off and the water phase concentrated. After cooling, the solid phase was filtered off and dried. 4.6 g (41 %) of di-(3-thienyl)iodonium tetrafluoroborate was obtained. The yield depends strongly upon how much the water phase is concentrated. For further purification the obtained salt was dissolved in water at about 20°. Most of the water was then evaporated and the obtained crystals filtered off and dried (m.p. 173-174°). Calcd. for $C_8H_6BF_4IS_2$ (378.0): I 33.4. Found: I 32.5.

Di-(3-thienyl)iodonium fluoride. To 10 g (0.030 mol) of di-(3-thienyl)iodonium chloride dissolved in 150 ml of boiling water, a silver fluoride solution prepared from silver oxide dissolved in 25 % hydrogen fluoride was added until no chloride ion was left. The disappearance of chloride ion was checked by adding a silver nitrate solution to an aliquote of the solution. The precipitated silver chloride was filtered off and the filtrate stored at room temperature for two days. It was then filtered and evaporated to almost dryness. The solid phase was filtered off, washed with ether and dried. 7.1 g (76 %) of di-(3-thienyl)iodonium fluoride (dec. slowly > 170°) was obtained. Elemental analysis for iodine gave too low a value, possibly due to the presence of crystal water.

Symmetrical difuryliodonium chlorides. General procedure.

2-Furyllithium,² 3-furyllithium³² and 2-(3-lithio-2-furyl)-1,3-dioxolane²⁷ solutions were prepared from 0.60 mol of furan or bromofuran in 100 ml of ether and 0.63 mol of commercial

butyllithium in hexane. These solutions were cooled to -70° and slowly added to 0.30 mol of trans-chlorovinylidioso dichloride⁴² in 400 ml of dry toluene, also cooled to -70° , at such a rate as to avoid ring-opening of 3-furyllithium. The reaction mixture was stirred at -70° for 2-3 hours, whereupon the cooling bath was removed. After the temperature had risen to 0° , the mixture was poured into water. The solid phase was filtered off, washed with water, acetone, and ether, dried and directly used for synthesis. Yields and analytical data are given in Tables 19 and 20. For longer periods the salts were stored at about -20° . Di-(2-furyl)iodonium chloride had, at times, a tendency to decompose at room temperature.

Symmetrical diselenienyliodonium chlorides. General procedure.

2-Selenienyllithium¹¹⁰ and 3-selenienyllithium^{11,111} solutions were prepared from 0.10 mol of selenophene or 3-bromo-selenophene¹¹¹ in 50 ml of ether and 0.11 mol of commercial butyllithium in hexane. These solutions were cooled to -70° and added to 0.050 mol of trans-chlorovinylidioso dichloride⁴² in 200 ml of dry toluene, also cooled to -70° , at such a rate as to avoid ring-opening of 3-selenienyllithium. After stirring for 2-3 hours the cooling bath was removed, and, after the temperature had risen to 0° , the mixture was poured into water. The solid phase was filtered off, washed with water, acetone, and ether, dried and directly used for synthesis. Yields and analytical data are given in Tables 19 and 20. To avoid decomposition the salts were stored at about -20° .

VI.5 Reactions of iodonium salts

Phenyl-2-thienyliodonium chloride and sodium nitrite. 0.20 g (0.62 mmol) of phenyl-2-thienyliodonium chloride, 0.21 g (3.0 mmol) of sodium nitrite and 6.0 ml of DMF in an ampoule were shaken for 4.0 hours at 110° in an oil-bath. The ampoule was opened, and after the addition of 1.00 ml of 0.143 M methanolic toluene solution as internal standard, the reaction mixture was analyzed by vpc. All products, except 2-chlorothiophene, were easily separated from DMF. That no chlorothiophene was formed could be verified if the reaction mixture was poured into water

and extracted with ether. The combined ether phases were washed with water and then analyzed by vpc. The results are given in Table 7. Columns: C, D.

Phenyl-3-thienyliodonium chloride and sodium nitrite. Using phenyl-3-thienyliodonium chloride, the reaction and analyses were performed as with phenyl-2-thienyliodonium chloride. The result is given in Table 7. Columns: C, D.

Phenyl-2-thienyliodonium chloride and sodium methoxide. 0.20 g (0.62 mmol) of phenyl-2-thienyliodonium chloride, 0.16 g (3.0 mmol) of sodium methoxide, and 6.0 ml of anhydrous methanol were shaken in an ampoule at 70° for 1.0 hours. The ampoule was opened and the content analyzed as above by vpc, yielding the result given in Table 7. Columns: C, D.

Phenyl-3-thienyliodonium chloride and sodium methoxide. Using phenyl-3-thienyliodonium chloride, the same method as with phenyl-2-thienyliodonium chloride was used. The result is given in Table 7. Columns: C, D.

Mesityl-thienyliodonium chlorides and sodium nitrite or methoxide. The reactions of mesityl-2-thienyl- and mesityl-3-thienyliodonium chloride and sodium nitrite or methoxide were performed under the same conditions and with the same relative concentrations as for the corresponding phenyl-thienyliodonium chlorides. The analyses were also performed in the same manner as above, giving the results as in Table 10. Columns: C, D.

Phenyl-2-thienyliodonium chloride and sodium sulphite. 0.75 g (2.3 mmol) of phenyl-2-thienyliodonium chloride, 2.3 g (10 mmol) of sodium sulphite ($\text{Na}_2\text{SO}_3 \cdot 7\text{H}_2\text{O}$), and 50 ml of water were stirred at reflux for 1 hour. After cooling, the water phase was extracted with ether. The combined ether phases were analyzed by vpc. It was found that the ether phase contained iodobenzene and 2-iodothiophene in a ratio of 2.3:1.0. Column: C.

Phenyl-[2-(2-(1,3-dioxolanyl))-3-furyl]iodonium chloride and sodium nitrite. To 4.0 g (60 mmol) of nitrobenzene was added, at 130°, 2.0 g of the unpure product obtained in the synthesis of phenyl-[2-(2-(1,3-dioxolanyl))-3-furyl]iodonium chloride (cf. above). After stirring at 130° for 1 hour, the reaction mixture was analyzed with combined vpc-mass spectrometry.

Besides nitrobenzene, iodobenzene and 2-(3-iodo-2-furyl)-1,3-dioxolane were the only products, which could be detected. This indicates that phenyl-furyliodonium chloride behaves with nitrite ion as phenyl-thienyliodonium chloride. Column: C.

Nitrothiophenes from symmetrical dithienyliodonium chlorides.

General procedure.

A. A solution of 10 mmol of dithienyliodonium chloride, and 50 mmol of sodium nitrite in 60 ml of DMF was stirred at 110° for 4-5 hours. After cooling, the reaction mixture was poured into water and extracted with ether. The combined ether phases were washed with water and dried over magnesium sulphate. The ether was evaporated and the residue chromatographed on neutral aluminium oxide. Elution with petroleum ether (b.p. $65-75^{\circ}$) gave the iodothiophene, whereupon the nitro compound was eluted with ether. The nitro compound could also be eluted with chloroform or benzene. The purity of the fractions was checked by vpc analysis. The nitro compounds were recrystallized from ethanol. Yields are given in Table 13, and analytical data in Tables 14 and 15. 2-Nitro- and 3-nitrothiophene were also isolated by using a different separation technique, described below. Columns: B, C.

B. 2-Nitro- and 3-nitrothiophene. 99 g (0.30 mol) of either di-(2-thienyl)- or di-(3-thienyl)iodonium chloride, 104 g (1.5 mol) of sodium nitrite, and 1500 ml of DMF were stirred at 130° for 4 hours. After cooling, the reaction mixture was poured into water and extracted with ether. The combined ether phases were washed with water and dried over magnesium sulphate. The ether was evaporated. When 300 ml of petroleum ether was added, 3-nitrothiophene precipitated. (2-Nitrothiophene did not precipitate without cooling.) After filtering the nitrothiophene, the filtrate was cooled to -70° ; more nitrothiophene precipitated and was filtered. The combined crops of nitrothiophene were washed with petroleum ether (b.p. $65-71^{\circ}$). After drying on a glass filter, 7.3 g of 2-nitrothiophene and 18 g of 3-nitrothiophene, respectively, were obtained.

The nitrothiophenes were, according to vpc, of more than 99 % purity. The isolated nitrothiophene was dissolved in boiling petroleum ether (b.p. $65-71^{\circ}$) with a small amount of neutral aluminum oxide added. Upon cooling to -70° the nitro-

thiophene fell out. After filtering and drying, the following yields and melting points were obtained: 2-Nitrothiophene, yield 5.4 g (14 %), m.p. 40.2-40.6°, lit. value: ^{88a} 40.5-41.5°; 3-nitrothiophene, yield 15 g (39 %), m.p. 75.0-75.4°, lit. value: ⁸⁹ 75.0-75.5°. It can be assumed, that this latter more convenient separation method is useful also for the preparation of other nitrothiophenes. In another run, di-(2-thienyl)iodonium chloride was added, at 110°, to the sodium nitrite in DMF. After stirring at 100-110° for 4 hours, work-up, and purification as in this latter alternative (B), 6.3 g (16 %) of 2-nitrothiophene was obtained. Column: C.

3-Formyl-4-nitrothiophene. To a solution of 0.50 g (2.5 mmol) of 2-(4-nitro-3-thienyl)-1,3-dioxolane in 50 ml of ether, 25 ml of 1.2 N hydrochloric acid was added, whereupon the mixture was stirred until vpc analysis showed that all acetal had disappeared (1.5 hours). The ether phase was separated, and the aqueous phase neutralized with sodium bicarbonate and extracted with ether. After drying, evaporation of the ether yielded 0.40 g (100 %) of 3-formyl-4-nitrothiophene, which was recrystallized from petroleum ether (b.p. 80-120°). Analytical data are given in Tables 14 and 15. Column: B.

Thiocyanothiophenes from symmetrical iodonium chloride. General procedure.

A solution of 0.030 mol of dithienyliodonium chloride, 0.15 mol of sodium thiocyanate, and 200 ml of DMF was stirred at 110-120° for 3 hours. After cooling, the reaction mixture was poured into water and extracted with ether. The ether phase was washed with water and dried over magnesium sulphate. In the case of 3-methylthio-4-thiocyanothiophene a pure product was not obtained directly upon distillation. The second fraction at 164-168°/11 mm was contaminated by 3-iodo-4-methylthiothiophene. Therefore, this fraction was dissolved in boiling petroleum ether (b.p. 40-60°), and after the solution was cooled to -70°, pure 3-methylthio-4-thiomethylthiophene (m.p. 47.8-48.4°) precipitated in 15 % yield. The same recrystallization procedure with the first fraction yielded another crop of 3-methylthio-4-thiomethylthiophene (m.p. 47.5-48.0°), raising the total yield to 23 %. For the other thiocyanothiophenes, distillation

gave pure products. The yields and analytical data for the thiocyanothiophenes are given in Tables 16, 17, and 18, respectively. Analytical samples were purified with preparative gas chromatography (BDS 20 %, Chrom. A 60/80, 3/8"x6'). Columns: C, E.

Di-(3-thienyl)iodonium chloride and diethyl malonate anion.

A. To 12 g (75 mmol) of diethylmalonate in 70 ml of DMF was added 2.0 g (50 mmol) of 55-60 % sodium hydride in oil. After stirring for 60 min, 3.3 g (10 mmol) of di-(3-thienyl)iodonium chloride was added. Stirring was continued for 50 hours at room temperature, whereupon the reaction mixture was poured into water, acidified and extracted with ether. Vpc analysis showed that thiophene and 3-iodothiophene had been formed, together with one further product. The mass spectrum of this latter product showed that no diethyl thienylmalonate had been obtained. Possibly, this unidentified product has its origin in ester condensations. Liquid ammonia as solvent likewise did not lead to the desired product. Columns: D, E.

B. In the reaction of 4.9 mmol of di-(3-thienyl)iodonium chloride, 27 mmol of sodium hydroxide, and 28 mmol of diethyl malonate in 50 ml of water in an ampoule at 110° for 26 hours, the same result as above was obtained. Columns: D, E.

C. To 0.60 g (11 mmol) of sodium methoxide in 60 ml of anhydrous methanol was added 1.8 g (11 mmol) of diethyl malonate. After stirring for 10 min, 2.2 g (22 mmol) of cuprous chloride and after an additional 5 min 3.6 g (11 mol) of di-(3-thienyl)-iodonium chloride were added. Stirring was continued at reflux for 3 hours. Vpc analysis indicated that thiophene, 3-chloro-, 3-methoxy- and 3-iodothiophene, but no diethyl thienylmalonate, had been formed. A corresponding run with 20 mmol of sodium methoxide, 20 mmol of diethyl malonate 4.0 mmol of copper sulphate and 20 mmol of di-(3-thienyl)iodonium chloride in 60 ml of anhydrous methanol gave the same result. Columns: D, E.

Di-(3-thienyl)iodonium chloride and ethyl sodiooxalacetate.

10 g (0.030 mol) of di-(3-thienyl)iodonium chloride, 31 g (0.15 mol) of ethyl sodiooxalacetate and 300 ml of water were stirred at reflux for 4 hours. After pouring into water and extraction with ether, the ether phase was analyzed by vpc. Preparative gas chromatography (OV 17, 15 %, Chrom. A 60/80,

3/8" x 6') and NMR analysis of collected product showed that no substituted thiophene other than 3-iodothiophene had been obtained. Nor did the addition of copper sulphate lead to diethyl thienylmalonate. Columns: D, E.

Di-(3-thienyl)iodonium tetrafluoroborate and fluoride ion.

0.21 g (0.55 mmol) of di-(3-thienyl)iodonium tetrafluoroborate, 0.23 g (4.0 mmol) of anhydrous potassium fluoride, and 6.0 ml of nitrobenzene, dried by distillation over phosphorous pentoxide, were shaken in an ampoule at 110° for 3 hours. The ampoule was opened and the reaction mixture analyzed. Only 3-iodothiophene was obtained. Any 3-fluorothiophene could not be detected. DMSO as solvent gave the same result. Nor did the corresponding reactions with sodium fluoride in DMF, acetonitrile or nitrobenzene lead to 3-fluorothiophene. Only 3-iodothiophene could be detected. The addition of copper sulphate in the reaction with potassium fluoride in water or DMSO was also unsuccessful in giving 3-fluorothiophene. The exchange of copper sulphate for disilverfluoride⁹⁴ did not afford any improvement. Columns: D, G.

Pyrolysis of di-(3-thienyl)iodonium fluoride. In a glass tube was placed a small amount of di-(3-thienyl)iodonium fluoride, whereupon the tube was sealed and placed in an oil-bath, at about 220°, until the content had decomposed. The tube was opened and the content washed out with ether. Vpc analysis of the ether phase indicated that only 3-iodothiophene had been formed. Any 3-fluorothiophene could not be detected. Columns: D, G.

3-Thienyl-phenyl ether. A solution of 20 g (0.061 mol) of di-(3-thienyl)iodonium chloride, 28 g (0.30 mol) of phenol, 12 g (0.30 mol) of sodium hydroxide, and 600 ml of water was stirred at reflux for 20 hours. More water was added and the water phase extracted with ether. The combined ether phases were washed with water, dilute sodium hydroxide solution, and water. After drying over magnesium sulphate, distillation gave 2.5 g (23 %) of 3-thienyl-phenyl ether at 133-134°/15 mm. An analytical sample was further purified by preparative gas chromatography (OV17, 15%, Chrom A 60/80, 3/8"x6'). Column: C. NMR (CDCl₃): Two quartets from the thiophene protons centered at $\delta = 6.49$ ppm for the

2-hydrogen and at $\delta = 6.78$ ppm for the 4-hydrogen. The thio-phenic 5-hydrogen and the phenyl hydrogens were not resolved (centered at 7.0 ppm). $J_{2,4} = 1.5$ Hz, $J_{2,5} = 3.2$ Hz, $J_{4,5} = 5.3$ Hz. Calcd. for $C_{10}H_8OS$ (176.2): C 68.2; H 4.58; S 18.2. Found: C 68.1; H 4.52; S 18.2.

3-Bromo- and 3-iodothiophene in the reaction with sodium phenoxide. To 100 ml of anhydrous methanol was added 6.0 g (0.26 mol) of sodium. When the hydrogen gas evolution had finished, 26 g (0.26 mol) of phenol was added followed by 15 g (0.092 mol) of 3-bromothiophene,⁹ 3.8 g (0.048 mol) of copper(II) oxide, and 0.10 g (0.60 mmol) of potassium iodide. After stirring at reflux for 96 hours the reaction mixture was analyzed by vpc. It was, however, found that only about 2 % of the 3-bromothiophene had been converted to 3-thienyl-phenyl ether. The same reaction in DMF at 50-60° using sodium hydride instead of sodium hydroxide as base gave, after 112 hours, no 3-thienyl-phenyl ether. The use of 3-iodothiophene⁵¹ instead of 3-bromothiophene did not lead to any improvement. Column: C.

3-Thienyl-phenyl sulphide. A solution of 20.0 g (0.0609 mol) of di-(3-thienyl)iodonium chloride, 29.0 g (0.260 mol) of thio-phenol, 10.5 g (0.260 mol) of sodium hydroxide, and 300 ml of water was stirred at reflux for 4.5 hours. After cooling, the reaction mixture was extracted with ether. The combined ether phases were washed with water, dilute sodium hydroxide solution, water, dried and distilled. 3.0 g (26 %) of 3-thienyl-phenyl sulphide was obtained at 167-169°/1 mm. Lit. values: 88-94°/0.3 mm⁹⁷ and 100-103°/0.3 mm.⁹⁸ Column: E. NMR ($CDCl_3$): δ_4 = centered at 7.00 ppm, $J_{2,4} = 1.8$ Hz, $J_{4,5} = 4.8$ Hz. Other couplings badly resolved.

Di-(3-thienyl)iodonium chloride and piperidyl anion. To 4.5 g (0.053 mol) of piperidine and 50 ml of acetonitrile was added 2.1 g (about 0.050 mol) of 55-60 % sodium hydride in oil. After stirring for 10 min, 3.3 g (0.010 mol) of di-(3-thienyl)iodonium chloride was added and stirring was continued at reflux for 4 hours. Vpc analysis of the reduction mixture indicated that no 3-piperidinothiophene had been formed. Some other more complex compounds had been formed. They could, however, not be identified with accuracy. If instead nitrobenzene was used as solvent

and the reaction performed at 110-120° for 3 hours, the products were thiophene, 3-iodothiophene, aniline and azoxybenzene. In the presence of cuprous chloride and with DMF as solvent only a small amount of 3-piperidinothiophene was produced, with side-reactions dominating. Columns: C, E.

Di-(3-thienyl)iodonium chloride and the anion of acetonitrile. To 10 g (about 0.25 mol) of 55-60 % sodium hydride in oil in 200 ml of acetonitrile was added 16.5 g (0.050 mol) of di-(3-thienyl)iodonium chloride. After stirring at reflux for 5 hours, the reaction mixture was analyzed by vpc. 3-Iodothiophene, but no thienylacetonitrile, could be detected. When copper sulphate was added, vpc and mass spectrometry indicated that possibly N-(3-thienyl)keteneimine and 1,1-di-(3-thienyl)acetonitrile had been formed. Columns: C, D, E.

2-Nitrofuran. 12 g (0.040 mol) of di-(2-furyl)iodonium chloride, 13 g (0.19 mol) of sodium nitrite, and 200 ml of DMF were stirred for 3 hours at 110-115°. After cooling, the reaction mixture was poured into water and extracted several times with ether. The combined ether phases were washed with water and dried over magnesium sulphate. Distillation gave 2-iodofuran, b.p. 45-49°/24 mm (lit. value:³⁰ 43-45°/15 mm), and 1.6 g (35 %) of 2-nitrofuran at 93-94°/24 mm. After further purification by preparative gas chromatography (OV 17, 15 %, Chrom. A 60/80, 3/8"x9') the 2-nitrofuran melted at 28.0-28.4°. Lit. value:¹⁰¹ 28.8-29.2°. Column: C. NMR [(CD₃)₂CO]: δ_3 = 7.54 ppm, δ_4 = 6.88 ppm, δ_5 = 7.89 ppm, $J_{3,5}$ = 1.0 Hz, $J_{3,4}$ = 3.7 Hz, $J_{4,5}$ = 1.9 Hz.

3-Nitrofuran. To 100 g of 1,3-dinitrobenzene warmed to 110°, 12 g (0.040 mol) of di-(3-furyl)iodonium chloride and 13 g (0.19 mol) of sodium nitrite were added. After stirring for 2 hours at 140°, distillation gave 3-iodofuran at 32-36°/22 mm (lit. value:³² 137-139°/765 mm), and 1.4 g (31 %) of 3-nitrofuran at 60-61°/18 mm, m.p. 26-27°. After further purification by preparative gas chromatography (OV 17, 15 %, Chrom. A 60/80, 3/8"x9') the 3-nitrofuran melted at 27.5-28.0°. Lit. value:¹⁰² 27°. Column: C. NMR [(CD₃)₂CO]: δ_2 = 8.65 ppm, δ_4 = 7.04 ppm, δ_5 = 7.75 ppm, $J_{2,5}$ = 1.7 Hz, $J_{2,4}$ = 0.8 Hz, $J_{4,5}$ = 2.1 Hz.

2-Nitroselenophene. 8.4 g (0.020 mol) of di-(2-selenienyl)-io-

donium chloride, 6.9 g (0.10 mol) of sodium nitrite and 150 ml of DMF were stirred for 3.5 hours at 110-120°. The reaction mixture was poured into water and extracted with ether. The combined ether phases were washed with water and dried over magnesium sulphate. After concentration, the residue was chromatographed on neutral aluminum oxide. 2-Iodoselenophene was eluted with petroleum ether (b.p. 40-60°), and 2-nitroselenophene with ether. The ether was removed, and 1.3 g (37 %) of 2-nitroselenophene was obtained. After recrystallization from ethanol, the 2-nitroselenophene melted at 33.4-33.7°. Lit. value:¹⁰⁴ 33.5-34°. From the petroleum ether solution, 2-iodoselenophene was obtained in 41 % yield, b.p. 89-91°/15 mm. Lit. value:¹⁵² 84-84.5°/11 mm. Column: C. NMR [(CD₃)₂CO]: δ_3 = 8.19 ppm, δ_4 = 7.39 ppm, δ_5 = 8.57 ppm, $J_{3,4}$ = 4.3 Hz, $J_{3,5}$ = 1.6 Hz, $J_{4,5}$ = 5.8 Hz.

3-Nitroselenophene. To 11 g (0.16 mol) of sodium nitrite in 300 ml of DMF, 12 g (0.028 mol) of di-(3-selenienyl)iodonium chloride was added at 110°. Stirring was continued for 1 hour at 110-120°. After work-up as above, the products were chromatographed on neutral aluminum oxide. 3-Iodoselenophene was eluted with petroleum ether (b.p. 40-60°), and 3-nitroselenophene with ether. After removal of the ether, 0.9 g (18 %) of 3-nitroselenophene was obtained, which after recrystallization from first ethanol and then petroleum ether (b.p. 40-60°), melted at 77.2-78.2°. Lit. value:¹⁰⁴ 77.5-78°. From the petroleum ether solution 3-iodoselenophene was obtained in 29 % yield at 106-107°/27 mm. Lit. value:¹⁵³ 56°/1 mm. Column: C. NMR [(CD₃)₂CO]: δ_2 = 9.29 ppm, δ_4 = 7.98 ppm, δ_5 = 8.29 ppm, $J_{2,4}$ = 1.5 Hz, $J_{2,5}$ = 2.8 Hz, $J_{4,5}$ = 5.8 Hz.

3-Thiocyanofuran. To 7.3 g (0.090 mol) of sodium thiocyanate and 100 ml of DMF, 9.0 g (0.030 mol) of di-(3-furyl)iodonium chloride was added at 110°. After stirring for 2 hours at 110-120°, 75 g of anhydrous sulpholane was added and the main part of the DMF distilled off, as the first fraction, at reduced pressure (12 mm). The next fraction (52-140°/12 mm) of about 10 g was collected for further purification. This fraction contained, according to vpc, 3-thiocyanofuran and DMF together with small amounts of 3-iodofuran and sulpholane. One further distillation gave two fractions. The first fraction at 53-71°/

12 mm contained 3-iodofuran, DMF, and a small amount of 3-thiocyanofuran, and the second at 71-79°/12 mm contained DMF and 3-thiocyanofuran. Preparative gas chromatography (BDS, 20 %, Chrom A 60/80, 3/8"x6'm) gave pure 3-thiocyanofuran. Column: C. NMR (CDCl₃): $\delta_2 = 7.74$ ppm, $\delta_4 = 6.62$ ppm, $\delta_5 = 7.57$ ppm, $J_{2,4} = 0.7$ Hz, $J_{2,5} = 1.5$ Hz, $J_{4,5} = 1.9$ Hz.

3-Thiocyanoselenophene. 13 g (0.031 mol) of di-(3-selenienyl)-iodonium chloride, 12 g (0.15 mol) of sodium thiocyanate, and 300 ml of DMF were stirred at 110° for 3 hours. The mixture was poured into water and extracted with ether. The combined ether phases were washed with water and dried over magnesium sulphate. Distillation gave 2.8 g (48 %) of 3-thiocyanoselenophene at 131-137°/15 mm. Column: C. NMR (CDCl₃): $\delta_2 = 8.24$ ppm, $\delta_4 = 7.40$ ppm, $\delta_5 = 8.11$ ppm, $J_{2,5} = 2.6$ Hz, $J_{2,4} = 1.4$ Hz, $J_{4,5} = 5.6$ Hz. Calcd. for C₅H₃NSSe (189.1): C 31.8; H 1.60; N 7.41. Found: C 31.5; H 1.61; N 7.16.

2-(3-Nitro-2-furyl)-1,3-dioxolane. To 13.8 g (0.200 mol) of sodium nitrite in 100 ml of nitrobenzene was added, at 110°, 17.6 g (0.0400 mol) of di-[2-(2-(1,3-dioxolanyl))-3-furyl]-iodonium chloride. After stirring for 1 hour at 90-110°, the reaction mixture was poured into water and extracted several times with ether. The combined ether phases were washed with water and dried over magnesium sulphate. After evaporation of the ether, the main part of the nitrobenzene was distilled off at reduced pressure under nitrogen. The residue was chromatographed on neutral aluminum oxide. The rest of the nitrobenzene and 2-(3-iodo-2-furyl)-1,3-dioxolane was eluted with petroleum ether (b.p. 40-75°) and 2-(3-nitro-2-furyl)-1,3-dioxolane with ether. Removal of the ether gave 5.0 g (68 %) of 2-(3-nitro-2-furyl)-1,3-dioxolane. This product, which contained a small amount of 3-nitro-2-furfural, was used for synthesis without further purification. Column: H. NMR (CDCl₃): $\delta_{\text{ring hydrogens}} = 7.25$ ppm and 7.41 ppm, $\delta_{\text{CH}} = 6.62$ ppm, $\delta_{\text{CH}_2\text{-CH}_2} = \text{centered at } 4.17$ ppm, $J_{4,5} = 2.0$ Hz.

3-Nitro-2-furfural. 4.9 g (26 mmol) of 2-(3-nitro-2-furyl)-1,3-dioxolane was dissolved in 50 ml of ether, and 200 ml of 2.5 N hydrogen chloride was added. After stirring for 1.5 hours,

no acetal could be detected by vpc. The reaction mixture was neutralized with sodium hydrogen carbonate solution. After separation of the ether phase, the water phase was extracted with ether. The combined ether phases were washed with water and dried over magnesium sulphate. Removal of the ether gave 3.2 g (87 %) of 3-nitro-2-furfural, which after recrystallization from petroleum ether, 40-60°. M.p. 70.8-71.8°. Column: H. NMR (CDCl₃): δ_4 = 7.11 ppm and δ_5 = 7.73 ppm, δ_{CHO} = 10.29 ppm, $J_{4,5}$ = 2.0 Hz, $J_{5,\text{CHO}}$ = 0.7 Hz, $J_{4,\text{CHO}}$ = not resolved. Calcd. for C₅H₃NO₄ (141.1): C 42.6; H 2.14; N 9.93. Found: C 42.9; H 2.30; N 9.79.

1-(3'-Nitro-2'-furfurylideneamino)hydantoin. 0.68 g (4.8 mmol) of 3-nitro-2-furfural, 0.73 g (4.8 mmol) of 1-aminohydantoin hydrachloride,¹¹² 5 ml of ethanol, and 10 ml of water were stirred at reflux for 40 min. After cooling, the yellow solid phase was filtered off, washed with water and dried. 1.1 g (96 %) of 1-(3'-nitro-2'-furfurylideneamino)hydantoin was obtained. M.p.: dec. > 280°. NMR (CDCl₃): δ_4 = 7.25 ppm. The 5'-hydrogen and the CH-hydrogen centered (doublet) at δ = 8.00 ppm. δ_{CH_2} = 4.47 ppm, δ_{NH} = 11.53 ppm, $J_{4',5'}$ = 2.0 Hz. Calcd. for C₈H₆N₄O₅ (238.2): C 40.3; H 2.54; N 23.5. Found: C 40.0; H 2.56; N 22.3.

Reaction between di-(3-thienyl)iodonium chloride and sodium cyanide. General procedure.

In a closed ampoule, ca. 0.20 g (0.61 mmol) of di-(3-thienyl)iodonium chloride, 0.16 g (3.3 mmol) of sodium cyanide, and 0.030-0.50 g (0.20-3.1 mmol) of cupric sulphate in 6.0 ml of water were shaken for 3-17 hours at 100° (oil-bath). After cooling to room temperature, the ampoules were opened. The contents were transferred to a separatory funnel. The ampoule was washed with ether, which was added to the reaction mixture. Additionally, 1.00 ml of 0.117 N methanolic toluene solution was added as internal standard. The ether phase was separated and the water phase extracted with ether. The combined ether phases were analyzed by vpc. The results are given in Table 22. Column: D.

Reaction between di-(3-thienyl)iodonium chloride and methanol.
General procedure.

In a closed ampoule, about 0.20 g (0.61 mmol) of di-(3-thienyl)iodonium chloride, 0.16 g (30 mmol) of sodium methoxide, 0.075-0.36 g (0.076-3.6 mmol) of cuprous chloride or 0.10-0.60 g (0.63-3.8 mmol) of cupric sulphate or 0.11-0.64 g (0.61-3.5 mmol) of 1,1-diphenylethylene in 6.0 ml of anhydrous methanol were shaken at 70°C for 1 hour (oil-bath). After cooling to room temperature, the ampoules were opened and 1.0 ml of 0.117 N methanolic toluene solution was added as internal standard and the mixture analyzed by vpc. The results are given in Tables 21 and 23. Column: D.

Reaction between di-(3-thienyl)iodonium chloride and piperidine.
General procedure.

In a closed ampoule, about 1.5 g (4.6 mmol) of di-(3-thienyl)iodonium chloride, 1.9 g (22 mmol) of piperidine, and 0.48-4.6 mmol of either a copper or sodium salt were shaken with 60 ml of water for 2-3 hours at 100°. After cooling to room temperature, the ampoules were opened. The contents were transferred to a separatory funnel and the ampoule washed with ether, which was added to the reaction mixture. Additionally, 1.00 ml of 0.117 N methanolic toluene solution was added as internal standard. The water phase was extracted with more ether. The combined ether phases were washed with water and analyzed by vpc. The results are given in Table 24. Column: D.

3-Piperidinothiophene. A solution of 21.0 g (0.064 mmol) of di-(3-thienyl)iodonium chloride, 1.6 g (0.0064 mol) of cupric sulphate pentahydrate, and 27 g (0.32 mol) of piperidine in 750 ml of water was refluxed with stirring for 2 hours. After cooling, the reaction mixture was extracted with ether and the combined ether phases extracted with dilute hydrochloric acid and water. The combined aqueous phases were made alkaline and extracted with ether. The combined ether phases were dried over magnesium sulphate and distilled to yield 1.6 g (15 %) of 3-piperidinothiophene, b.p. 130-131°/17 mm. The product had the same NMR spectrum as the sample, b.p. 64-66°/0.3 mm, described by Wynberg et al.¹⁵⁴ Column: D.

2-Methoxyfuran.

A. To 11 g (0.20 mol) of sodium methoxide in 300 ml of anhydrous methanol, 50 g (0.28 mol) of 1,1-diphenylethylene was added and thereafter 21 g (0.071 mol) of di-(2-furyl)iodonium chloride. After reflux for 1.5 hours the reaction mixture was poured onto ice and extracted several times with ether. The combined ether phases were washed with water and dried over magnesium sulphate. Distillation gave 1.4 g (20 %) of 2-methoxyfuran at 113-116° (lit. value:¹⁵⁵ 110-111°), containing about 10 % of 2-iodofuran. Column: C.

B. To 8.1 g (0.15 mol) of sodium methoxide and 3.0 g (0.030 mol) of cuprous chloride in 200 ml of anhydrous methanol, 9.0 g (0.030 mol) of di-(2-furyl)iodonium chloride was added. After reflux for 1 hour the reaction mixture was, after cooling, poured into water and extracted several times with ether. The combined ether phases were washed with water and dried over magnesium sulphate. The ether phase was concentrated to 30-40 ml. In addition to ether, this residue contained 2-methoxy- and 2-iodofuran. After cooling to -70°, 0.79 M ethyllithium in ether was added until the 2-iodofuran was consumed as checked by vpc. Protonation was performed with methanol. After pouring into water, the mixture was extracted with ether. The combined ether phases were dried over magnesium sulphate. Distillation gave 0.3 g (10 %) of pure 2-methoxyfuran at 108-110°. Lit. value:¹⁵⁵ 110-111°. Column: C.

3-Thienyl-1-hexyl ether. To 200 ml of *n*-hexanol, 5.7 g (0.25 mol) of sodium was added. When the evolution of hydrogen gas had finished, 7.9 g (0.049 mol) of anhydrous copper sulphate was added followed by 16 g (0.049 mol) of di-(3-thienyl)iodonium chloride. After stirring at 110° for 1.5 hours the reaction mixture was poured into water and extracted with ether. The combined ether phases were washed with water and dried over magnesium sulphate. Distillation gave 2.1 g (23 %) of 3-thienyl-1-hexyl ether at 119-123°/16 mm. Column: C. NMR (CDCl₃): $\delta_2 = 6.25$ ppm, $\delta_4 = 6.75$ ppm, $\delta_5 = 7.15$ ppm, $\delta_{\text{O-CH}_2} = 3.93$ ppm, $\delta_{(\text{CH}_2)_4} = 1.36$ ppm, $\delta_{\text{CH}_3} = 0.90$ ppm, $J_{2,4} = 1.5$ Hz, $J_{2,5} = 3.1$ Hz, $J_{4,5} = 5.2$ Hz, $J_{\text{-O-CH}_2\text{-CH}_2\text{-}} = 6.0$ Hz. Other

couplings were not resolved. Calcd. for $C_{10}H_{16}OS$ (184.3): C 65.2; H 8.75; S 17.4. Found: C 65.3; H 8.77; S 16.7.

3-Chlorothiophene. 15 g (0.046 mol) of di-(3-thienyl)iodonium chloride, 14 g (0.24 mol) of sodium chloride, 7.4 g (0.046 mol) of anhydrous copper sulphate, and 250 ml of DMF were stirred at 110° for 3 hours. After cooling, the reaction mixture was poured into water and worked up as above. Distillation gave 2.9 g (53 %) of 3-chlorothiophene at $136-142^{\circ}$. Lit. value:⁷⁰ $133-135^{\circ}$.

3-Furyl-phenyl ether. To 11 g (0.12 mol) of phenol, 4.8 g (0.12 mol) of sodium hydroxide, 4.0 g (0.040 mol) of cuprous chloride, and 200 ml of methanol was added 12 g (0.040 mol) of di-(3-furyl)iodonium chloride. After stirring at reflux for 1 hour, the reaction mixture was, after cooling, filtered, poured into water, and extracted with ether. The combined ether phases were washed with dilute sodium hydroxide solution, water, and dried over magnesium sulphate. Distillation gave 0.1 g (2 %) of ca. 90 % pure 3-furyl-phenyl ether at $92-96^{\circ}/11$ mm. Column: C. NMR ($CDCl_3$): Furan hydrogens centered at $\delta = 6.24$ ppm, $\delta = 7.05$ ppm, and $\delta = 7.15$ ppm. Phenyl protons centered at $\delta = 7.24$ ppm. Couplings were badly resolved.

CIDNP experiments. The following solutions were prepared: 2.5 M sodium methoxide in methanol, 2.5 M sodium ethoxide in ethanol, 2.5 M sodium n-propoxide in n-propanol, 2.5 M n-butoxide in n-butanol, saturated sodium nitrite in DMF, 0.10 M di-(3-thienyl)iodonium chloride in DMSO, 0.20 M di-(3-thienyl)iodonium tetrafluoroborate in DMSO, saturated di-(3-thienyl)iodonium chloride in DMF.

On recording the NMR spectra, 0.30 ml of a iodonium salt solution was added with a syringe to 0.30 ml of a solution containing one of the nucleophiles in a NMR tube already placed in the apparatus (a Varian A-60 instrument). Scanning was started immediately after the addition. and was repeated about each five seconds over the region where the aromatic absorptions were expected. Alkoxide ions as nucleophiles were found to give either enhanced absorption or emission, with a maximum in a shorter time than 30 seconds. Nitrite ions as nucleophile did not show any CIDNP effects. When cuprous chloride was added to the sodium butoxide solution, before adding the di-(3-thienyl)-

iodonium chloride in DMSO, the emission signals were cancelled. During the reactions with the alkoxides the temperature was held at about 40°, while the reaction with sodium nitrite was performed at 100°. Di-(3-thienyl)iodonium chloride and the tetrafluoroborate gave rise to the same effects. The results are further discussed in section V.6.

Pyrolysis of phenyl-3-thienyliodonium chloride. A small amount of phenyl-3-thienyliodonium chloride was placed in a glass tube of 20 cm length, sealed in one end. About 5 cm of the sealed end of the tube was immersed into an oil-bath at 235±5°. The other part of the tube was used as an air condenser. When the reaction was complete, the content was washed out with ether. Vpc analysis of the ether phase indicated the formation of chlorobenzene, 3-chlorothiophene, iodobenzene, and 3-iodothiophene in a ratio of 4.1:1.1:1.1:4.1. Column: C.

Di-(3-thienyl)iodonium chloride and sodium thiocyanate in the presence of copper sulphate. 1.7 g (5.2 mmol) of di-(3-thienyl)iodonium chloride and 1.3 g (16 mmol) of sodium thiocyanate were reacted at 70-110° in DMF or DMSO in the presence of varying amounts of anhydrous copper sulphate. Besides 3-iodothiophene, which was formed in all reactions, combined vpc-mass spectrometry indicated that the addition of copper sulphate favored the formation of 3-chloro- and 3-isothiocyanothiophene, lowering the yield of 3-thiocyanothiophene, obtained in the uncatalyzed reaction. The reaction is further discussed in section V.5. Column: D.

REFERENCES

1. Gilman, H. and Shirley, D.A., J. Am. Chem. Soc. 71, 1870 (1949).
2. Ramanathan, V. and Levine, R., J. Org. Chem. 27, 1216 (1962).
3. Gronowitz, S. and Sörlin, G., Acta Chem. Scand. 15, 1419 (1961).
4. Gronowitz, S., Advances in Heterocyclic Chemistry, Vol. 1 (Ed. A.R. Katritzky), Academic Press, New York and London, 1963, pp. 1-124.
5. Gronowitz, S., Organic Compounds of Sulphur, Selenium and Tellurium, Vol. 2, The Chemical Society, London, 1973, pp. 352-525.
6. Klayman, D. and Günther, W.H.H., Organic Selenium Compounds, John Wiley and Sons, New York (1973).
7. Fringuelli, F. and Taticchi, A., J.C.S. Perkin Trans. I 199 (1972).
8. Gronowitz, S., Arkiv Kemi 7, 361 (1954).
9. Gronowitz, S., Acta Chem. Scand. 13, 1045 (1959).
10. Mack, W., Angew. Chem. 77, 260 (1965).
11. Gronowitz, S. and Frejd, T., Int. J. Sulfur Chem. A, 2, 165 (1972).
12. Gronowitz, S. and Frejd, T., Acta Chem. Scand. 23, 2540 (1969).
13. Gronowitz, S. and Frejd, T., Acta Chem. Scand. 24, 2656 (1970).
14. Paulmier, C., Morel, J., and Pastour, P., Bull. Soc. Chim. France 2511 (1969).
15. Morel, J., Paulmier, C., and Pastour, P., Compt. Rend. C, 269, 37 (1969).
16. Steinkopf, W. and Köhler, W., Ann. (Liebig) 532, 250 (1937).
17. Steinkopf, W., Die Chemie des Thiophens, Verlag von Theodor Steinkopf, Dresden and Leipzig, 1941.
18. Campaigne, E. and LeSuer, W.M., J. Am. Chem. Soc. 70, 415 (1948).
19. Hirao, I., Yakugaku Zasshi (J. Pharm. Soc. Japan) 73, 1023 (1953); Chem. Abstr. 48, 10723 (1954).

20. Rosenberg, J., Ber. 18, 1773 (1885).
21. Gronowitz, S., Moses, P., and Håkansson, R., Arkiv Kemi 16, 267 (1961).
22. Terent'ev, A.P., Bel'enkii, L.I., and Yanovskaya, L.A., J. Gen. Chem. USSR (Engl. transl.) 24, 1251 (1954).
23. Wirth, H.O., Königstein, O., and Kern, W., Ann. (Liebig) 634, 84 (1960).
24. Gronowitz, S. and Vilks, V., Arkiv Kemi 21, 191 (1964).
25. Steinkopf, W., Schmitt, H.F., and Fiedler, H., Ann. (Liebig) 527, 237 (1937).
26. Wright, G.F. and Gilman, H., Ind. Eng. Chem. 40, 1517 (1948).
27. Gronowitz, S. and Michael, U., Arkiv Kemi 32, 283 (1970).
28. Zaluski, M.-C., Robba, M., and Bonhomme, M., Bull. Soc. Chim. France 1838 (1970).
29. Šrogl, J., Janda, M., and Stibor, I., Coll. Czech. Chem. Comm. 35, 3478 (1970).
30. Gilman, H., Mallory, H.E., and Wright, G.F., J. Am. Chem. Soc. 54, 733 (1932).
31. Gilman, H. and Wright, G.F., J. Am. Chem. Soc. 55, 3302 (1933).
32. Gronowitz, S. and Sörlin, G., Arkiv Kemi 19, 515 (1963).
33. Magdesieva, N.N., Advances in Heterocyclic Chemistry, Vol. 12 (Eds. A.R. Katritzky and A.J. Boulton), Academic Press, New York and London, 1971, pp. 1-41.
34. Hartman, C. and Meyer, V., Ber. 27, 426 (1894).
35. Lucas, H.J. and Kennedy, E.R., Organic Syntheses, Vol. 22, 52 (1942).
36. Beringer, F.M., Drexler, M., Gindler, E.M., and Lumpkin, C.C., J. Am. Chem. Soc. 75, 2705 (1953).
37. Fichter, F. and Stern, S., Helv. Chim. Acta 11, 1256 (1928).
38. Beringer, F.M., Bachofner, H.E., Falk, R.A., and Leff, M., J. Am. Chem. Soc. 80, 4279 (1958).
39. Beringer, F.M., Dehn, J.W., Jr., and Winicov, M., J. Am. Chem. Soc. 82, 2948 (1960).
40. Nesmeyanov, A.N., Bull. Acad. Sci. U.R.S.S. Classe Sci. Chim. 239 (1945); Chem. Abstr. 40, 2122 (1946).
41. Beringer, F.M., Falk, R.A., Karniol, M., Lillien, I.,

- Masullo, G., Mausner, M., and Sommer, E., J. Am. Chem. Soc. 81, 342 (1959).
42. Beringer, F.M. and Nathan, R.A., J. Org. Chem. 34, 685 (1969).
43. Beringer, F.M. and Nathan, R.A., J. Org. Chem. 35, 2095 (1970).
44. Beringer, F.M., Brierley, A., Drexler, M., Gindler, E.M., and Lumpkin, C.C., J. Am. Chem. Soc. 75, 2708 (1953).
45. Beringer, F.M., Forgione, P.S., and Yudis, M.D., Tetrahedron 8, 49 (1960).
46. Eisch, J.J., Advances in Heterocyclic Chemistry, Vol. 7 (Eds. A.R. Katritzky and A.J. Boulton), Academic Press, New York and London, 1966, pp. 1-37.
47. Mallan, J.M. and Bebb, R.L., Chem. Rev. 69, 2, 693 (1969).
48. Sandin, R.B., Chem. Rev. 32, 249 (1943).
49. Banks, D.F., Chem. Rev. 66, 243 (1966).
50. Bachmann, G.B. and Heisye, L.V., J. Am. Chem. Soc. 70, 2378 (1948).
51. Gronowitz, S. and Håkansson, R., Arkiv Kemi 16, 309 (1961).
52. Yom-Tov, B. and Gronowitz, S., Chemica Scripta 3, 37 (1973).
53. Gronowitz, S. and Dahlgren, K., Arkiv Kemi 21, 201 (1964).
54. Lawesson, S.-O., Arkiv Kemi 11, 317 (1957).
55. Gronowitz, S. and Holm, B., Acta Chem. Scand. 23, 2207 (1969).
56. Gronowitz, S. and Karlsson, L., Acta Chem. Scand. 17, 2120 (1963).
57. Gronowitz, S., Gjøs, N., Kellogg, R.M., and Wynberg, H., J. Org. Chem. 32, 463 (1967).
58. Gjøs, N., Ph.D. Thesis, University of Lund, Sweden (1971).
59. Gjøs, N. and Gronowitz, S., Acta Chem. Scand. 26, 1851 (1972).
60. Pearson, R.E. and Martin, J.C., J. Am. Chem. Soc. 85, 354 (1963).
61. Moses, P. and Gronowitz, S., Arkiv Kemi 18, 119 (1962).
62. Jones, R.G. and Gilman, H., Org. Reactions 6, 339 (1951).
63. Gronowitz, S., Moses, P., and Håkansson, R., Arkiv Kemi 16, 267 (1961).
64. Gilman, H. and Gorsich, D., J. Am. Chem. Soc. 79, 2625 (1957).
65. Rosén, U., Personal communication.

66. Wittig, G. and Rings, M., Ann. (Liebig) 719, 127 (1968).
67. Reinecke, M.G. and Adickes, H.W., J. Am. Chem. Soc. 90, 511 (1968).
68. Campaigne, E. and LeSuer, W.M., J. Am. Chem. Soc. 71, 333 (1949).
69. Campaigne, E. and Bourgeois, R.C., J. Am. Chem. Soc. 76, 2445 (1954).
70. Gronowitz, S. and Rosén, U., Chemica Scripta 1, 33 (1971).
71. Gronowitz, S., Svenson, R., Bondesson, G., Magnusson, O., and Stjernström, N.E., Acta Pharm. Suecica 11, 211 (1974).
72. Frejd, T., Personal communication.
73. Gronowitz, S. and Frejd, T., To be published.
74. Corey, E.J., Pure Appl. Chem. 14, 19 (1967).
75. Corey, E.J. and Seebach, D., Angew. Chem. Int. Ed. Engl. 4, 1075 (1965).
76. Nesmeyanov, A.N., Perevalova, E.G., Golovnya, R.V., and Shilovtseva, L.S., Doklady Akad. Nauk SSSR 102, 535 (1955).
77. Nesmeyanov, A.N., Perevalova, E.G., Tyurin, V.D., and Gubin, S.P., Izvest. Akad. Nauk SSSR, Ser. Khim. 1938 (1966).
78. Lucas, H.J. and Kennedy, E.R., Org. Syntheses, Coll. Vol. III, 482 (1955).
79. Melander, L., Arkiv Kemi 8, 361 (1956).
80. Beringer, F.M. and Forgiione, P.S., Tetrahedron 19, 739 (1963).
81. Willgerodt, C. and Roggatz, H., J. prakt. Chem. 1, 423 (1900).
82. Yamada, Y. and Okawara, M., Bull. Chem. Soc. Japan 45, 2515 (1972).
83. Yamada, Y. and Okawara, M., Bull. Chem. Soc. Japan 45, 1860 (1972).
84. Gronowitz, S. and Liljefors, S., To be published.
85. Gronowitz, S., Moses, P., Hörnfeldt, A.-B., and Håkansson, R., Arkiv Kemi 17, 165 (1961).
86. Gronowitz, S., Biezais, A., and Mathiasson, B., Arkiv Kemi 21, 265 (1964).
87. Gronowitz, S. and Holm, B., Chemica Scripta 2, 245 (1972).
88. a) Östman, B., Acta Chem. Scand. 22, 1687 (1968).
b) Maag, H. and Manukian, B.K., Helv. Chim. Acta 56, 178 (1973).
89. Blatt, A.H., Bach, S., and Kresch, L.W., J. Org. Chem. 22, 1693 (1957).

90. Östman, B., Arkiv Kemi 19, 499 (1963).
91. Nishimura, S., Motoyama, R., and Imoto, E., Bull. Univ. Osaka Prefect, Ser. A 6, 127 (1958).
92. Campaigne, E. and Patrick, R.L., J. Am. Chem. Soc. 77, 5425 (1955).
93. Caserio, M.C., Glusker, D.L., and Roberts, J.D., J. Am. Chem. Soc. 81, 336 (1959).
94. Poyer, L., Fiedler, M., Harrison, H., and Bryant, B.E., Inorg. Syntheses 5, 18 (1957).
95. Gronowitz, S., Arkiv Kemi 12, 239 (1958).
96. Crowder, J.R., Glover, E.E., Grundon, M.F., and Kaempfen, H.X., J. Chem. Soc. 457c (1963).
97. Kellogg, R.M., Schaap, A.P., Harper, E.T., and Wynberg, H., J. Org. Chem. 33, 2902 (1968).
98. Gronowitz, S. and Håkansson, R., Arkiv Kemi 17, 73 (1961).
99. Marquis, R., Ann. Chim. Phys. 4, 216 (1905).
100. Rinkes, I.J., Rec. Trav. Chim. 49, 1169 (1930).
101. Freuere, B.T. and Johnson, J.R., J. Am. Chem. Soc. 53, 1142 (1931).
102. Rinkes, I.J., Rec. Trav. Chim. 57, 390 (1938).
103. Umezawa, S., Bull. Chem. Soc. Japan 11, 775 (1936).
104. Yur'ev, Yu.K. and Zaitzeva, E.L., J. Gen. Chem. USSR (Engl. transl.) 29, 1057 (1959).
105. Yur'ev, Yu.K., Zaitzeva, E.L., and Kozantzev, G.G., J. Gen. Chem. USSR (Engl. transl.) 30, 2189 (1960).
106. Outurgin, F., Ah-kow, G., and Paulmier, C., Compt. Rend. C, 277, 29 (1973).
107. Yur'ev, Yu.K. and Zaitzeva, E.L., J. Gen. Chem. USSR (Engl. transl.) 30, 873 (1960).
108. Umezawa, S., Bull. Chem. Soc. Japan 12, 4 (1937).
109. Gronowitz, S. and Holm, B., Synth. Comm. 4, 63 (1974).
110. Yur'ev, Yu.K. and Sadovaya, N.K., J. Gen. Chem. USSR (Engl. transl.) 34, 1814 (1964).
111. Yur'ev, Yu.K., Sadovaya, N.K., and Grekova, E.A., J. Gen. Chem. (Engl. transl.) 34, 841 (1964).
112. Jack, D., J. Pharm. Pharmacol. 11, 108 (1959).
113. Astra AB, Research Laboratories, Södertälje, Sweden, Personal communication.

114. Dodd, M.C., Cramer, D.L., and Ward, W.C., J. Am. Pharm. Ass. 39, 313 (1950).
115. Beringer, F.M., Galton, S.A., and Huang, S.J., J. Am. Chem. Soc. 84, 2819 (1962).
116. Beringer, F.M. and Falk, R.A., J. Chem. Soc. 4442 (1964).
117. McEwen, W.E., Lubinkowski, J.J., and Knapczyk, J.W., Tetrahedron Lett. 3301 (1972).
118. Beringer, F.M., Gindler, E.M., Rapoport, M., and Taylor, R.J., J. Am. Chem. Soc. 81, 351 (1959).
119. Knapczyk, J.W., Lubinkowski, J.J., and McEwen, W.E., Tetrahedron Lett. 3739 (1972).
120. Foster, D.L.D., Hobbs, P.D., and Magnus, P.D., Tetrahedron Lett. 4793 (1972).
121. Lubinkowski, J.J. and McEwen, W.E., Tetrahedron Lett. 4817 (1972).
122. Bacon, R.G.R. and Hill, H.A.O., Quart. Rev. 19, 95 (1965).
123. Beringer, F.M., Geering, E.J., Kuntz, I., and Mausner, M., J. Phys. Chem. 60, 141 (1956).
124. Gronowitz, S. and Holm, B., Chemica Scripta 6, 133 (1974).
125. Jones, E. and Moodie, I.M., Tetrahedron 21, 2413 (1965).
126. Manly, D.G. and Amstutz, E.D., J. Org. Chem. 21, 516 (1956).
127. D'Alelio, G.F., Williams, C.J., Jr., and Wilson, C.L., J. Org. Chem. 25, 1028 (1960).
128. Gronowitz, S., Hörnfeldt, A.-B., and Pettersson, K., Synth. Comm. 3, 213 (1973).
129. a) Cohen, T., Wood, J., and Dietz, A.G., Jr., Tetrahedron Lett. 3555 (1974).
b) Beringer, F.M. and Bodlaender, P., J. Org. Chem. 34, 1981 (1969).
130. Sandin, R.B., Christiansen, R.G., Brown, R.K., and Kirkwood, S., J. Am. Chem. Soc. 69, 1550 (1947).
131. Beringer, F.M. and Gindler, E.M., J. Am. Chem. Soc. 77, 3203 (1955).
132. Beringer, F.M. and Mausner, M., J. Am. Chem. Soc. 80, 4535 (1958).
133. Beringer, F.M. and Huang, S.J., J. Org. Chem. 29, 445 (1964).

134. Guanti, G., Dell'Erba, C., and Macera, P., J. Heterocyclic Chem. 8, 537 (1971).
135. Fischer, H. and Bargon, J., Accounts Chem. Res. 2, 110 (1969).
136. Ward, H.R., J. Am. Chem. Soc. 89, 5517 (1967).
137. Ward, H.R. and Lawler, R.G., J. Am. Chem. Soc. 89, 5518 (1967).
138. Lawler, H.G., J. Am. Chem. Soc. 89, 5519 (1967).
139. Bargon, J. and Fischer, H., Z. Naturforsch. 22a, 1556 (1967).
140. Buchachenko, A.L. and Zhidomirov, F.M., Russ. Chem. Rev. 801 (1971).
141. Ward, H.R., Accounts Chem. Res. 5, 18 (1972).
142. Lawler, R.G., Accounts Chem. Res. 5, 25 (1972).
143. Closs, G.L., J. Am. Chem. Soc. 91, 4552 (1969).
144. Closs, G.L. and Trifunac, A.D., J. Am. Chem. Soc. 92, 2183 (1970).
145. Kaptein, R., J. Chem. Soc. D, 732 (1971).
146. Kaptein, R. and Oosterhoff, L.J., Chem. Phys. Lett. 4, 195 (1969).
147. Kaptein, R. and Oosterhoff, L.J., Chem. Phys. Lett. 4, 214 (1969).
148. Brokken-Zijp, J. and van de Bogaert, H., Tetrahedron Lett. 249 (1974).
149. Kiprianova, L.A., Levit, A.F., Gragerov, I.P., and Buchachenko, A.L., Teor. Eksp. Khim. 9, 508 (1973).
150. Steinkopf, W., Jacob, H. and Penz, H., Ann. (Liebig) 512, 136 (1934).
151. Steinkopf, W., Schmitt, H.F., and Fiedler, H., Ann. (Liebig) 527, 237 (1937).
152. Yur'ev, Yu.K. and Sadovaya, N.K., Zhur. Obshchei. Khim. 26, 3154 (1956).
153. Paulmier, C. and Pastour, P., Compt. Rend. C, 265, 926 (1967).
154. Buiter, F.A., Sperna Weiland, J.H., and Wynberg, H., Rec. Trav. Chim. 83, 1160 (1964).
155. Petfield, R.J. and Amstutz, E.D., J. Org. Chem. 19, 1944 (1954).

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